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ABSTRACT

Sodium amobarbital (Amytal), sodium pentobarbital (Nembutal) and sodium thiopental (Pentothal) are capable of decreasing the cardiac output of dogs and increasing the total peripheral resistance of the systemic arterial tree. In dogs under light anesthesia from each of these drugs, a supplemental dose of 10 mg./kg. of body weight of the respective drug decreased cardiac output an average 28.4% in the case of Amytal, 17.2% with Nembutal, and 19.7% with Pentothal. At moderate levels of anesthesia, a supplemental dose of only 5 mg./kg. usually decreased the cardiac output. The decrease in output was accompanied by an increase of total peripheral resistance of even greater magnitude; in dogs receiving 10 mg./kg. supplemental doses, these increases in resistance amounted to 30% with Amytal, 32% with Nembutal, and 38% with Pentothal. In view of the frequent use of barbiturate anesthesia in animal experiments, the magnitude of these hemodynamic changes makes careful anesthesia imperative, lest experimental results be distorted. The frequently-used dose of 30 mg./kg. of Nembutal for induction of anesthesia appears to be too great. In our experiments, ascent of dogs from moderately deep to light anesthesia was accompanied by an increase in cardiac output and a decrease in total peripheral

resistance; the latter, however, did not increase in proportion to the increase in output, a lag which may be associated with increased sympathetic nervous system activity under barbiturate anesthesia. The administration of small doses of Pentothal frequently resulted in cardiac arrhythmia or a sudden, marked increase in pulmonary artery pressure.

Creation of aorto-caval fistulas 4 to 13 mm. in length resulted in elevation of end diastolic pressures in both left and right ventricles. This increase in pressure, indicating myocardial failure, frequently occurred within 24 hours after creation of the fistula. In most experiments, the left and right ventricles failed simultaneously; however, in one or two dogs, the right ventricle may not have failed quite as quickly as the left. The increase of pressure in the left ventricle was usually proportionately greater than that in the right, perhaps due to the greater mass and resistance to filling of the left ventricle. Some dogs showed a striking parallel between the ventricles in pressure changes as failure developed. Cardiac output increased immediately upon formation of the fistula; there was a subsequent further increase related to increased blood volume and increased end diastolic pressures. Output fell as failure became severe. Autopsy findings varied, depending on the acuteness and severity of failure, and whether the failure was primarily "congestive" or "myocardial."

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THE UNIVERSITY OF ALBERTA

II. HEMODYNAMIC CHANGES IN HIGH-OUTPUT CARDIAC FAILURE

A DISSERTATION

SUBMITTED TO THE SCHOOL OF GRADUATE STUDIES
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE
OF MASTER OF ..SCIENCE.....

FACULTY OF MEDICINE

DEPARTMENT OF MEDICINE

by

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ACKNOWLEDGMENTS

These investigations were carried out with the aid of a grant from the Canadian Life Insurance Officers' Fund, under the direction of Dr. R.S. Fraser, with whom it was a real pleasure to have been associated.

The author is grateful to Mrs. Eileen Klymak, without whose technical and other assistance not nearly so great a volume of work could have been completed. It is a pleasure to acknowledge the assistance of Dr. Kenneth Bradshaw for similar reasons. The surgical help of Dr. Colin Ross is greatly appreciated. Thanks are offered to Dr. H.E. Rawlinson for statistical advice, and to Mr. Charles Heath for his valuable comments on methods and procedures.

THE PROBLEM

During the course of previous studies of hemodynamics in dogs, certain variations occurred which were felt to be due to the use of barbiturate anesthetics. Because the voluminous literature on the subject of barbiturates was frequently at odds regarding the effect of these drugs on hemodynamics, particularly of animals, it was felt desirable to determine for ourselves what these effects might be. Hence, this thesis is divided into two portions, Part I dealing with the effects of three barbiturates on the hemodynamics of dogs, and Part II dealing with a continuation of a previous study, to observe the hemodynamic changes which occur in dogs following the creation of a fistula between the aorta and the inferior vena cava below the renal arteries. The particular changes which we wished to observe were the changes in end diastolic pressure in the left and right ventricles, to determine the manner in which the ventricles fail.

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Despite the widespread use of barbiturate drugs for many years in human anesthesia and in animal experimentation, the action of this group of drugs on many physiological parameters is not fully understood. Frequently in biological experiments, the possible influence of barbiturates on the results of the experiment are considered only superficially or not at all, perhaps due to such statements as Rushmer's, that "the circulatory system of the anesthetized dog is stable."²⁹ Some of the effects of barbiturates, particularly on the central nervous and respiratory systems, have been intensively investigated, but it has not been until recent years, with the great advances in medical technology, that some of the less well understood effects of the barbiturate drugs have been more adequately investigated. Despite these advances, confusion still exists, particularly regarding the effect of barbiturates on the circulatory system. Some of this confusion is due to differences among the various barbiturate drugs, as well as to varying effects of these drugs on different species.

The effects of barbiturate on cardiac output and peripheral resistance have shown a wide divergence of results on experimental animals, but studies in humans have shown a better agreement so that it is convenient to consider the effects of these drugs on the human circulatory system first. Man is far easier to anesthetize than laboratory animals and hence requires much smaller doses of barbiturates³³. Li et al.,¹⁷ in human beings during Pentothal anesthesia, noted a 25% decrease in the cardiac index at surgical levels of anesthesia. In a comprehensive study at the Mayo Clinic, Fieldman⁴ et al. found that induction with Pentothal anesthesia to light electroencephalographic levels decreased cardiac index by 24%, and when anesthesia was deepened the cardiac index showed a further decrease of 24% of the values found at the lighter levels. However, on return to lighter levels after deep anesthesia, the cardiac index showed no significant systematic return to

higher values over an average period of 25 minutes. The stroke index decreased 27% at light levels of anesthesia with a further mean decrease of 24% when anesthesia was deep. On return to lighter levels after deep anesthesia, stroke index increased by 18%. The radial artery blood pressure decreased an average of 19%, with a range from 5 - 42%, but no further significant systematic change in mean arterial pressure was observed when the depth of anesthesia was increased. No further systematic change in arterial pressure was observed when the patients were allowed to return to lighter levels of anesthesia, although wide variability was noted. There was a high significance in the decrease of systolic arterial pressure, depending on whether induction of anesthesia was rapid or slow. The mean decrease in systolic arterial pressure was 23% in those patients receiving rapid induction, compared to a mean decrease of only 8% in those patients in whom induction was slow. In all patients, the decrease in blood pressure occurred within 90 seconds after the onset of induction and some return toward pre-anesthetic levels was noted in all patients within three minutes. The decrease in pressure was greatest in those patients who had the highest mean pressures prior to induction of anesthesia. Regarding cardiac rate, no significant systematic changes were observed in patients during induction of anesthesia, during deep anesthesia, or during emergence from deep anesthesia. All patients showed a significant decrease in the estimated "central blood volume" after induction, and a further decrease occurred in all patients when anesthesia was deepened. However, on emergence from deep anesthesia, a significant increase was not observed in the central blood volume, these values paralleled those obtained for the cardiac index. The mean peripheral resistance did not change during induction to light levels of anesthesia, but the peripheral resistance increased when the depth of anesthesia was increased. On emergence from deeper

levels of anesthesia, no significant systematic change in the peripheral resistance was observed. Central venous pressure changes were equivocal during pentothal and nitrous oxide anesthesia. Increases in central venous pressure were observed during induction to light levels of anesthesia, while decreases were observed when anesthesia was deepened. These changes were on the border of statistical significance. Systematic change in the central venous pressure was not observed on emergence from deep anesthesia. The pH of arterial blood decreased in direct proportion to the depth of anesthesia unless respiration was assisted; it increased on emergence from anesthesia. In those patients in whom apnea was produced, controlled respiration increased pH. Regarding arterial oxygen saturation, during induction a mean decrease of 11% in arterial oxygen saturation was noted in three patients in whom anesthesia was induced while they breathed room air; the saturation rapidly returned to values of more than 98% as soon as the mixture of nitrous oxide and oxygen was added. The remaining patients in this study underwent induction with Pentothal after they had breathed 100% oxygen for a minimum of 8 minutes and a decrease in arterial oxygen saturation did not occur in any of these patients. In five patients, respiration was manually assisted because of depth of anesthesia. The pH of arterial blood increased in all of these patients. The maintenance of positive pressure in the airway was associated with a decrease of pressure in the radial artery and an increase in the central venous pressure; these values immediately returned to original levels on release of the positive pressure. Only one patient showed electrocardiographic changes even at deep levels of anesthesia. The blood pressure of this patient suddenly increased from 154/88 mm. of mercury to 210/127 mm. as anesthesia was deepened and a bigeminal pulse developed. This disappeared as soon as anesthesia was lightened. A few other studies of barbiturate

anesthesia in human beings are available which agree with these findings of decreased cardiac output, decreased arterial oxygen saturation during induction, and increase in blood pH with respiratory acidosis (see 3,4).

Regarding another barbiturate, Winchell et al.³⁸ found that administration of Sodium Amytal to hypertensive and normotensive human beings decreased the cardiac output and increased the peripheral resistance. These authors commented that the use of Sodium Amytal as a test for fixed hypertension was therefore invalid.

The effect of barbiturates on the hemodynamics of animals has largely been confined to dogs, and the results have not been consistent. It is generally agreed that administration of barbiturates causes a fall in arterial blood pressure, particularly if the barbiturate is administered rapidly. Slowly administered Pentothal, however, may give a rise in arterial blood pressure¹⁰. Lockett²⁰ found that deep Nembutal anesthesia lowered the blood pressure but that light Nembutal anesthesia increased the blood pressure over pre anesthetic levels. Most authors agree that after induction of anesthesia with barbiturate, in dogs, the arterial blood pressure returns to normal levels²⁴. Regarding heart rate, most authors agree that Nembutal and Amytal increase the heart rate of dogs²⁴ and cats³³. However, Lockett¹⁹ found that Nembutal did not increase the heart rate of normal atropinized dogs but slowed the heart rate of sympathectomized dogs; she concluded that there must be an increase in activity of the sympathetic nervous system with Nembutal anesthesia. Amytal and Nembutal exert a vagal blocking effect^{11,18} and it has been suggested that the increase in heart rate with the administration of barbiturates may be due to this effect. It has been suggested that Pentothal may irritate the cardiac vagus¹¹.

The situation regarding cardiac output is even more confusing, and for a variety of reasons. Some authors have attempted to use trained,

unanesthetized dogs for control readings before induction of barbiturate anesthesia, but Bredel² has found that the resting cardiac output of trained dogs varies considerably from day to day, and Wiggers³⁵ has commented on the difficulties in using unanesthetized dogs: "The dog is an animal which responds with tremendous variations in heart rate and blood pressure to trivial auditory, visual, and surface stimuli, as well as to psychic influences. The latter may be minimized by training, but, despite claims to the contrary, cannot be eliminated entirely for studies of cardiovascular problems. Page et al.²⁶ found no change in cardiac output with Nembutal anesthesia. While some authors state that the cardiac output during barbiturate anesthesia remains relatively constant, if the anesthetic level remains constant^{7,36}, other authors disagree^{24,30,34}. In a recent paper, Nash et al.²⁴ found that the cardiac output during Nembutal anesthesia fell markedly; they found that the cardiac output fell steadily during the first two hours of anesthesia, remained stable for 2 - 3 hours, and then over a three hour period gradually rose. In another communication³⁹, this group stated that Pentothal anesthesia produced a progressive decrease in the cardiac output reaching a minimum after two hours of anesthesia; the value remained significantly low for the next two hours of anesthesia. These authors stated that an increase in peripheral resistance accompanied the decrease in cardiac output, with the mean arterial blood pressure and heart rate remaining fairly steady throughout 7 hours of anesthesia. Foltz et al.⁵ abandoned the use of straight Nembutal anesthesia because repeat cardiac output determinations after 30 minutes following a previous determination yielded decreased cardiac output with increase in total peripheral resistance. Griffin et al.⁹ concluded that the cardiac output of the anesthetized dog was constantly shifting, varying about 12%. H. C. Wiggers³⁶

stated that the cardiac output varied with the blood pressure level but not with the heart rate, and stated that if the blood pressure remained constant, so did the cardiac output. Vidt et al.³⁴ have recently stated that there is considerable spontaneous variability of the cardiac output in dogs anesthetized with Nembutal. Greisheimer's group^{8(a),(b)} continues to report that dogs anesthetized with Pentothal and other ultra-short acting barbiturates show a progressive increase in cardiac output, decrease in peripheral resistance, and rise in blood pressure.

This variation in findings is disturbing when one considers the tremendous number of experiments which are carried out under the assumption that the circulatory system of the dog is stable during anesthesia. The results of studies on human would lead on to expect similar findings in dogs. Gruber's¹⁰ observation that all barbiturates cause dilatation of the heart chambers with decrease in forced contraction of the auricles and ventricles would also lead one to believe that the cardiac output is depressed with barbiturates. However, when one considers the many changes which occur with anesthesia some of the variations in findings may perhaps be explained. These changes are probably most marked with deep anesthesia, and as Nash et al.²⁴ have stated, the widely used anesthetic dose of 30 mgs. of Nembutal per kilogram of body weight seems needlessly high. Suskind and Rahn³² administered 25 mgms. of Nembutal per kilogram of body weight and noted that the anesthesia in their dogs was deeper than is usually obtained with such a dose, the animals being depressed to the level of cessation of the eye reflex. At this depth, they found a marked depression of respiration, both the total minute volume and the rate of respiration being diminished by approximately 45% from the recovery value. This large respiratory change was followed by a decrease in the alveolar pO_2 to a minimum value of 76 mm. in the first 30 minutes following the intravenous injection of anesthetic and at the same time the pCO_2

increased to 42.3 mm. Within the next 30 minutes the respiration was stimulated enough so that the pO₂ rose to 90 mm. but the pCO₂ still continued to rise to a maximum of 44.4 mm. The arterial blood gas changes paralleled those in the alveoli. The effects of barbiturates on the autonomic nervous system have been mentioned. Some of the variations in reported cardiac output changes might be due to the method employed. Thus, the use of the direct Fick method in animals which are not in a steady state (as in deep anesthesia) has been criticized (see 6). Similarly the use of a dye dilution method may be unreliable depending on respiratory rate, the sinus arrhythmia which occurs in dogs etc., since a dye output determination requires only about 10 seconds. Assisted respiration cannot be used to correct hypoxia and hyperapnea because it is well known that positive pressure respiration decreases the cardiac output ²¹.

It is interesting that Foltz et al.⁵ commented that the circulatory status of the dog under Nembutal anesthesia is comparable to moderate or exercise levels of activity. Because of their finding of decreased cardiac output on successive determinations and because of considerable variation in the response of animals to barbiturate anesthetics, this group abandoned Nembutal anesthesia in favor of a mixture of equal volumes of Nembutal and Dial-urethane solution, administered about one hour after the administration of morphine. They found that this anesthetic with morphine uniformly produces slow cardiac rates with sinus arrhythmia characteristic of resting or sleeping dogs, and while the cardiac output values were lower than with Nembutal anesthesia, the dogs remained in a more stable, basal state of circulatory activity. These authors noted that the total peripheral resistance was higher with the mixed anesthetic agent.

Other effects of barbiturates which have been described in dogs,^{40,41} rats¹⁶, and other animals include engorgement of the spleen, with trapping of

red blood cells and consequent depression of hemoglobin and hematocrit values, decrease in serum proteins, and increase²⁴ or decrease³¹ in plasma volume. In human beings, Price et al.²⁷ found an average 6% increase in plasma volume with morphine premedication and an average 3% increase in plasma volume with Pentothal-nitrous oxide anesthesia.

With these many variables in mind, our studies on dogs have been carried out under light Nembutal anesthesia, since light anesthesia entails less respiratory depression and there is less likelihood of other changes (e.g. blood volume³¹) than under deep anesthesia. This frequently necessitates the administration of small supplemental doses of barbiturate during the experiment to keep the animal asleep. We therefore decided to determine the effects of small increments of three barbiturates on the cardiac output, peripheral resistance, and other hemodynamic variables in dogs.

METHODS

The experiments were performed on eight male and female mongrel dogs weighing 15 to 23 kg. The number of animals was restricted so that the effects of the three barbiturates employed might be compared in the same animals. Four dogs (numbers 25, 27, 28, and 29) were used for the majority of experiments, extending over a 4-month period, but four other animals were used occasionally to permit the other group adequate periods between anesthetics. Dogs 25, 27, 28 and 29 were intact and apparently healthy, as was Dog 30; the latter animal was used late in the course of the project, for reasons to be mentioned in the text. Dog 18, used twice, Dog 20, used once, and Dog 26, used once, had unilateral subcutaneous carotid artery transplants and left ventriculopexies (see Section II) created several weeks or months previously; we have found that these procedures do not affect the animals' health.

Pressure pulses in the right atrium, right ventricle, and pulmonary artery were measured using a No. 5 cardiac catheter attached to a Statham P23D strain gauge. A Sanborn Polyviso 4-channel recorder was used. Femoral artery pressures were obtained with a No. 18 gauge needle attached to a 47 cm. length of saline-filled plastic tubing with an internal diameter of 1.6 mm. The tubing was attached via a stopcock assembly to another strain gauge. Both the No. 5 catheter and the plastic tube assemblies gave adequate frequency responses to in vitro sine wave impulses. The reference level (zero) for pressure pulse recording was the estimated level of the right atrium of each dog; once estimated, this same level was used for all experiments.

Electrocardiograms were recorded simultaneously with pressure pulses in all but two or three of the first experiments. Hypodermic needles were attached to brass plugs which were screwed to the electrocardiograph

cable tips; the hypodermic needles were inserted subcutaneously to serve as electrodes. The right and left leg leads were reversed to provide an electrocardiogram with deflections similar to those of human E.C.G.'s.

Oxygen saturations of heart chamber and arterial blood were measured with a whole blood cuvette oximeter and single scale galvanometer control assembly^{*}. This apparatus was checked one to three times weekly on blood samples on which oxygen saturations were also determined by the method of Van Slyke and Neill.

Cardiac outputs were determined by the dye dilution method¹³ using Evans' blue (T-1824) dye. Known amounts of dye were injected from a calibrated syringe through the cardiac catheter into the pulmonary artery or right ventricle as rapidly as possible (1 to 1.5 seconds). Arterial blood was withdrawn through the cuvette oximeter²⁵ which was connected via our own control box assembly[#] to a mirror-type galvanometer[@] and optical recorder. The presence of increasing and then decreasing amounts of dye in the blood withdrawn through the oximeter altered the output of the oximeter photocells, the attached galvanometer deflecting and providing the usual type of cardiac output curve on the recorder. A calibration curve was obtained by drawing through the oximeter, 5 c.c. aliquots of blood previously obtained from the femoral artery, to which known amounts of dye were added by a micrometer syringe[£]. Four aliquots of blood were used to construct the calibration curve, containing concentrations of 0, 10, 20, and 40 mg. of T-1824 dye per liter of whole blood. The use of whole blood made hematocrit correction unnecessary. Nevertheless, hematocrits were obtained on arterial blood in virtually all experiments, the blood being centrifuged in Wintrobe tubes for 30 minutes at 1,500 revolutions per minute; the hematocrit checks enabled us

^{*}Manufactured by the Waters Corp., Rochester, Minn.

[#]Constructed by Prof. K. Newbound of the U. of A. Physics Dept.

[@]Manufactured by Dr. B. Large, Berlin, Germany (Multiflex Galvanometer MG1a).

[£]"Agle" syringe, Burroughs-Wellcome Co., Montreal.

to determine that regeneration of blood cells was occurring satisfactorily in each dog.

Because the Waters Corp. control assembly does not provide sufficient sensitivity for the transcription of satisfactory dye curves, we used our own control box, as mentioned. The Waters Corp. assembly bucks the output of the oximeter infrared photocell against the output of the red cell, providing a stable baseline for dye curves not influenced by hemoglobin changes. Other workers feel that this bucking is not necessary for these minor fluctuations. The relatively large amounts of dye which we used would tend to minimize such minor variations, so we sacrificed the bucking arrangement for the greater sensitivity of our own control box.

All our experiments used dogs under light anesthesia, with arterial blood oxygen saturations of 90% or higher, because reduced hemoglobin interferes with light absorption by the dye.

The cuvette oximeter does not yield a calibration curve which is linear with increasing quantities of dye, but rather a curve which progressively flattens as the amount of dye is increased. Therefore all curves were replotted off the calibration curve, before extrapolation of the descending limb on semilogarithmic paper after the method of Hamilton. The mean concentration of the dye during its first circulation was obtained by tracing the curve on high grade paper. This curve was then cut out with fine scissors. A 10 cm.

square of paper adjacent to the curve was also cut out. Both were weighed, and the ratio weight of curve/weight of 100 sq. cm. of paper X 100 sq. cm. yielded the area of the curve. This area was divided by the base of the curve yielding a hypothetical rectangle, the base of which was the base of the output curve, and the height of which was mean concentration of dye over the period of circulation of dye. The error of this method, on a small number of repeat determinations, was of the order of 2 to 3% (or 20 to 30 c.c. per liter for a 2 to 3 liter/minute cardiac output curve).

An attempt was made to determine blood volumes using the oximeter-whole blood technique. Following injection of dye for cardiac output, an alarm clock was set for 10 minutes. Dye remaining in the catheter was flushed into the dog using the heparinized (4,000 units/liter) saline drip employed to keep the catheter clot free. At the appropriate times, blood was withdrawn through the cuvette and recorded on the same paper as the cardiac output curve and calibration curve. The 10 minute concentration of dye was used to calculate blood volume, according to the usual formula (dye injected/concentration), where the "dye injected" was the sum of the dye injected for the cardiac output curve plus the flushed residual dye in the catheter, and "concentration" was the concentration determined from the galvanometer deflection from the 10 minute blood sample. A few blood volumes were determined in unanesthetized and anesthetized dogs for comparison with the whole blood, photographic method.

All experiments, including the control group, were performed at random intervals and in no fixed order, employing the above methods as routinely used in our laboratory. Time, and the administration of anesthetic, were the particular factors of importance in this series of experiments.

In all, forty-five experiments were performed, two of which were unsatisfactory for technical reasons. The experiments included three main groups: one employing sodium amobarbital (Amytal) as the anesthetic, one

with sodium pentobarbital (Nembutal), and one with sodium thiopental (Pentothal). Each of these groups was subdivided, approximately one-half of each group receiving an increment of 5 mg. per kg. body weight of the anesthetic agent, the other half receiving 10 mg. per kg. Briefly, the experiments were as follows:— The animal was anesthetized with the particular barbiturate, receiving a calculated dose of 20 - 25 mg. per kg. This quantity was administered intravenously, slowly, and the amount necessary varied considerably from animal to animal, and to a lesser extent from experiment to experiment in the same animal. Variations were also due to the type of barbiturate, more Amytal being required to produce anesthesia than Nembutal or Pentothal. The barbiturate, obtained in powder form, was freshly mixed in distilled water for each experiment. Following this slowly-administered dose, the needle was left in the vein for several minutes while the anesthetic agent took effect. Muscle relaxation, the blink reflex, and reaction to mild pain stimuli were checked, as well as the dog's respiratory rate and amplitude. Clinical judgment was used, further barbiturate being injected a few milligrams at a time until adequate muscle relaxation, and regular thoracic breathing, were obtained. The dog was then placed on its back on the experimental table, tied loosely in position with the neck well extended, and under direct vision, a plastic endotracheal tube was placed between the vocal cords. The recording equipment, previously switched on, was permitted about 30 minutes for warming up. Hair was shaved from the neck and groin of the dog. A No. 13 gauge hollow-ground needle was inserted into an external jugular vein, the No. 5 catheter threaded through its lumen, and a slow heparinized saline drip begun to keep the catheter free of blood clot. Arterial puncture was performed with an 18-gauge needle, connected to the plastic tubing, and taped in place. The electrocardiograph needle-electrodes were inserted subcutaneously and an E.C.G. recorded (bipolar and

unipolar limb leads). During these procedures, the depth of anesthesia of the dog was noted, and small supplemental doses administered if the dog responded excessively to pain, if muscle relaxation was not adequate, if the dog began coughing the endotracheal tube, or if respirations became rapid.

This preparation required 30 to 45 minutes. Oxygen saturations were then determined on blood drawn from the jugular vein, superior vena cava, pulmonary artery, and femoral artery. Occasionally, if respiration was depressed more than usual, oxygen saturation of arterial blood oscillated between, for example, 85 and 95 per cent, rising to the latter value with each respiration and then drifting slowly downward. In these cases, a suitable time was waited until the depth of anesthesia decreased and arterial blood remained more than 90 per cent saturated with oxygen. The position of the catheter tip for withdrawal of blood was determined by the contour of pressure pulses monitored on the Sanborn recorder. Fluoroscopic control was not found necessary for passing intracardiac catheters in dogs. Following the determination of oxygen saturations, the cuvette oximeter was connected to our own control box and galvanometer. Blood was withdrawn (about 22 c.c.) from the artery into a syringe containing dry heparin for calibration purposes and hematocrit determination. Usually the increments of dye were added to the aliquots of blood immediately and the galvanometer deflections of the calibration curve recorded. Pressure pulses were recorded again, and the catheter position in the pulmonary artery (or, occasionally, right ventricle) confirmed. Withdrawal of blood from the artery at a steady rate, through the oximeter, was begun; rate of withdrawal was 30 to 40 c.c. per minute. Dye was injected rapidly from the calibrated syringe into the catheter and a clock set. Recording of the galvanometer beam position was begun at the commencement of injection; recording was ceased when recirculation of dye began, as noted by the path traversed by the light beam on the galvanometer control panel.

Pressure pulses were immediately recorded on the Sanborn Polyviso recorder. At appropriate times (10 minutes in these experiments), blood was withdrawn through the oximeter for the blood volume estimations. All blood withdrawn for the cardiac outputs or blood volumes was reinjected into the dog. Pressure pulses were again recorded and then, with continuous recording at a slow rate of speed of the artery pressure pulse a 5 or 10 mg. per kg. increment of the barbiturate was injected in $2\frac{1}{2}\%$ solution through the cardiac catheter into the pulmonary artery or right ventricle. The time was noted which had elapsed since the previous cardiac output determination, and the clock re-set; beginning and end of injection were marked on the continuously recorded arterial pressure pulse. The cardiac catheter stopcock was then switched into the strain gauge, and continuous recording begun of the pulmonary artery (or right ventricular) pressure pulse. In most experiments, pressures were recorded from the other chambers of the right heart at this time. The peripheral arterial and right heart pressures were recorded continuously at a slow speed, except for brief moments to flush out the catheter or arterial needle when clotting appeared to be occurring. After an average time of 12 minutes (range 10 to 30 minutes), another cardiac output-pulse pressure-blood volume set of readings were taken. Since the dogs were generally at a light stage of anesthesia at the time of injection of barbiturate, the additional dose seldom depressed the animals sufficiently to interfere with recording of output curves. When this did occur, the second set of readings were deferred until respiratory variation of oxygen saturation was virtually normal. Despite the fact that waiting might permit the animal to become light enough that any effect of the barbiturate on the cardiac output might have passed, the waiting was necessary not only to eliminate base-line wavering due to uneven blood oxygen saturation, but because increased amounts of reduced hemoglobin decrease the effect of Evans'

blue dye, since reduced hemoglobin absorbs light at the same wave length (620 Angstrom units) as the dye. Just as a man's shadow is more sharply defined in the bright sunlight than on a cloudy day, so is the galvanometer deflection greater when the dye is present in oxyhemoglobin, rather than in decreased light-transmitting reduced hemoglobin.

In the control series, the second set of determinations were obtained at an average time of 16 minutes after the first set of readings (range 14 to 30 minutes). This time was set arbitrarily to be somewhat longer than the interval between the first cardiac output and injection of barbiturate (12 minutes). Any change of cardiac output in the experimental series would then have occurred from the same level of anesthesia and from the equivalent time at which the second output was determined in the control group.

Following the second set of readings, the E.C.G. needle electrodes were removed, the catheter and indwelling 13-gauge needle were removed and the jugular vein held lightly for a few minutes to prevent any bleeding; the arterial needle was removed and the artery held moderately firmly for 5 or more minutes until there was no sign of bleeding.

The balance of the strain gauges and the zero line of the recorder were checked frequently during the experiments; unbalancing of the gauges was seldomly noted, since adequate warm-up time was allowed before the experiments, but the zero lines sometimes changed, particularly the gauge connected to the catheter-stopcock assembly, since this was manipulated more, particularly during injection of barbiturate. At the end of each experiment, both gauges were calibrated against a mercury manometer.

Although tolerance to barbiturate is known to occur²⁸, our experiments were spaced sufficiently that there appeared to be no danger of this occurring. It has been stated that almost daily Nembutal anesthesia in dogs

produces no tolerance ⁴².

Calculations

Cardiac output was calculated by the formula:

$$F = \frac{60I}{Ct}$$

where F is the flow rate (cardiac output in liters per minute), I is the amount of dye injected into the catheter, C is the mean concentration of dye during the first circulation (i.e. mean concentration of the extrapolated curve), and t is the time required for this first circulation.

Total peripheral resistance was computed as:

$$\frac{\text{Mean B.P. in mm. Hg.} \times 60}{\text{Cardiac output in c.c./min.}}$$

and expressed in large units (P.R.U.). The mean blood pressure was obtained by electric integration of arterial pressure pulses on the Sanborn recorder.

Total pulmonary resistance was computed in similar fashion, and also expressed as large units (P.R.U.).

RESULTS

Control Series: These experiments were performed at random intervals during other work in the laboratory rather than at one time so that no subconscious changes in techniques might occur with the knowledge that this was a "control" series. Hence, in the course of another experiment in which the same parameters were being measured (see Section II), a second set of determinations were performed on Dog 26 (Table I, Experiment 1). Similarly, the use of Dog 27 three times in this control series was not planned; in one way, this was fortuitous, for it illustrates the variability in quantity of barbiturate anesthetic required by the same animal from time to time, as well as the variation in response of various hemodynamic parameters.

Anesthesia: Although three barbiturate drugs were used in the experimental series, the control animals were anesthetized only with Nembutal, for two reasons: (1) the main purpose of the experiment was to determine the effect of increments of drug administered during anesthesia, and (2) we had postulated, on evidence from the literature and from experience, that all three barbiturates act similarly on the cardiovascular system of dogs, as far as the physiologic parameters which we are interested in are concerned.

The mean anesthetizing dose of Nembutal was 28.4 mg./kg. of body weight. All dogs were under light anesthesia, except Dog 27 (Table I, Experiment 5) which was somewhat deeper than usual (see below). The dose for each dog represents the total amount of barbiturate given before the first cardiac output was determined, i.e., initial anesthetizing dose plus all supplemental doses necessary to maintain a reasonably even anesthesia.

Cardiac Output: The second cardiac output determination (COII) was carried out an average of 16 minutes after the first (COI). The average of the first and second determinations is virtually identical. Although in Experiments 2

TABLE I

19.

Hemodynamic Findings in Dogs Under
Nembutal Anesthesia (Control Series).

Experiment No.	Dog Number	Weight in Kg.	Dose of Nembutal Before COI (MG. Per Kg.)	Initial Determinations				Determinations Associated With First Cardiac Output				
				Heart Rate Beats/Minute	Pressures s/d,m in MM. HG.			Cardiac Output (C.O.I) in Liters/Min.	Heart Rate Beats/Min.	Pressure s/d,m in MM. HG.		
					Right Ventricle	Pulmonary Artery	Femoral Artery			Right Ventricle	Pulmonary Artery	Femoral Artery
1	26	14.3	43.7	155	44-2 12	28 8 18	170 102 134	3.76	173	47-2 14	28 8 18	190 116 153*
2	27	15.9	18.9	156	24 0 6	23 7 14	188 108 140	2.87	156	26-1 8	24 4 13	193 117 145
3	25	22.7	26.4	96	23-1 5	22 5 11	208 117 144	3.87	166	20-2 8	20 6 12	246 156 185
4	27	16.0	28.1	130	29 1 9	24 7 14	199 124 149	2.15	172	26 1 9	22 7 14	202 126 145
5	27	16.2	24.7	170	27-1 8	24 8 14	220 150 171	1.78	175	23-2 7	21 5 13	212 146 171
Mean				17.0	28.4	141.4	142 147.6	2.89	168		140 159.8	
Standard Deviation					±9.3	±29.2	±25 ±14.2	±0.94	±7.7		±23 ±17.6	

Total Pulmonary Resistance in Units (T.P.R.I)	Total Peripheral Resistance in Units (T.P.R.I)	Determinations Associated With Second Cardiac Output										Total Pulmonary Resistance (T.P.R.II) in Units	Total Peripheral Resistance (T.P.R.II) in Units
		Cardiac Output (COI) in Liters/Min.	Heart Rate Beats/Min.	Pressures In Mm. Hg. s/d. m									
				Right Ventricle	Pulmonary Artery		Femoral Artery						
0.287	2.44	3.76	190	14	18	151*		0.287	2.41				
0.272	3.03	2.49	168	28 0	10	25 4	13	199 126	150	0.313	3.61		
0.186	2.87	3.80	192	24 -2	8	23 6	12	256 163	192	0.189	3.03		
0.391	4.05	2.59	200	32 -1	14	26 9	16	202 126	150	0.371	3.47		
0.438	5.76	1.70	180	26 -1	9	25 7	15	214 140	164	0.529	5.79		
0.315	3.63	2.88	186			14.8		161.4		0.338	3.66		
±0.100	±1.33	±0.90	±12.3			±2.4		±18.1		±0.126	±1.27		

* Carotid Artery Pressure.

and 4, the second cardiac output fell 13% and rose 20% respectively, little or no change occurred in the other three experiments. In this control group, the average of changes between the first and second cardiac outputs was $\pm 8\%$, but the net change in output of the five dogs was only 1%. To determine whether the changes which occurred in each dog (not between the group means) were significant, the "t" test for paired differences was applied. $t = 0.137$, and $P \gg 0.5$. It seems safe to conclude that, after about one hour of Nembutal anesthesia, during an average 16-minute period, there was no significant change in cardiac output determined by the dye dilution method.

Peripheral Resistance: Table I shows that the mean change in total peripheral resistance was negligible between the two determinations, although the change in each dog varied between -1.2% (Exp. 1) and +19.1% (Exp. 2). The average change was $\pm 8.1\%$, and the net change only 1.3%. On application of the "t" test for paired differences, $t = 0.172$ and $P \gg 0.5$, indicating that there was absolutely no significance in the changes which occurred in the group as a whole under the circumstances of the experiment. The changes are probably due to a combination of the random variations which must be expected in biological experiments, and any errors inherent in our methods.

Since the calculation of total peripheral resistance depends on the value for the cardiac output, which we have mentioned, and the mean arterial blood pressure, no further comments are necessary regarding blood pressure changes, which remained fairly stable.

Heart Rate: The heart rate increased from a mean value of 141.4 beats per minute during "initial" determinations to a mean value of 168 at the time of determinations associated with the first cardiac output (CO I). This is understandable, and a frequent finding in our experience, because in our experiments the first recordings of E.C.G. and pulse pressures were begun

after only about 30 minutes of anesthesia, when the animals were usually under somewhat deeper anesthesia and therefore not in a stable state. However, the increase in heart rate to 186 beats per minute during COII determinations was unexpected. Application of the "t" test for paired differences revealed that $t = 4.112$ and $P < 0.02$, a finding which is at least suspicious if not significant. In working with barbiturate-anesthetized dogs, it has been our impression that the onset of sinus tachycardia after the slower pulse rates of the early, deeper period of anesthesia is an indication that the dog is becoming lighter, even though respirations may not have changed in rate or amplitude and reflex responses have not changed. In this control series, the increase in heart rate from COI to COII determinations suggests that the animals were gradually coming out of their anesthesia, even though the cardiac outputs and total peripheral resistance values were virtually unchanged. If this is true, then there must be a lag period before the cardiac output also changes; such a lag period has been reported in humans ascending from deep to light anesthesia⁴, as we have mentioned.

In this regard, it is interesting that our protocols note that Dog 27 was rather deeper than usual in Experiment 5 (Table I). This is reflected by the lower cardiac output and higher total peripheral resistance values than in Experiments 2 and 4 employing the same dog. In Experiment 5, the pulse rate changed less than in any of the other four experiments in this series. Regarding Experiment 4, in addition to an increase in heart rate, there was an increase in the cardiac output together with a decrease in total peripheral resistance despite a small increase in the arterial blood pressure; these findings almost undoubtedly mean that the animal was in lighter anesthesia for COII than for COI determinations.

Total Pulmonary Resistance: Table I indicates that a small increase in this value occurred, but statistical analysis attributes no significance to the

change ($t = 1.150$, $P > 0.1$).

Experimental Series: The results are summarized in Tables II and III.

Anesthesia: As with the control group, the figures given for dosage of barbiturates are the sums of initial doses and incremental doses administered early in each experiment before COI determinations. No barbiturate was injected after the COI determinations, except the 5 or 10 mg. supplement. Because we attempted at all times to maintain the dogs at light levels of anesthesia, occasionally after the COI determinations, during the blood volume waiting period, the dog would become quite light, with occasional stretching movements, tension of muscles, and very rapid breathing. Regardless, no further anesthetic was administered until the 5 or 10 mg. supplement. In view of this fact, it is perhaps not surprising that in many of the experiments in which 5 mg. supplements were injected, the various determinations (cardiac output, heart rate, etc.) remained at the same level as the COI determinations or increased despite the 5 mg. supplemental dose. However, since the purpose of the experiment was to determine the effect of such doses, this problem of sudden lightening or anesthesia provided additional opportunity for observation.

In Experiments 6 and 27, following the administration of the barbiturate supplement and the COII determinations, another increment of barbiturate was given and a third set (CO III) of determinations taken. Regarding Experiment 27, the dog was deeper than usual for the CO I readings, so the supplement was administered in small increments over several minutes to ensure that too much respiratory depression did not ensue. Similarly, after the CO II determinations in this case, a longer time than usual was waited before the supplementary dose was injected, to permit metabolism of some of the drug already given and improve respiration.

[illegible]

[illegible]

* Arrhythmia developed (see text)

For Paired Differences (T.P.R.II - T.P.E.I), $t = 2.63$, $P < 0.0$

The anesthetizing dosages of Nembutal and Pentothal ranged from 21.3 to 30.0 mg./kg. (mean values), which are within the range usually mentioned in the literature. However, again it should be stressed that these total dosage figures include small incremental doses given during the initial period of anesthesia (approximately 30 minutes). In our experience, initial anesthetizing doses of more than 20 mg./kg. frequently cause severe respiratory depression, introducing the variables of hypoxia, CO₂ retention, blood pH changes, etc., which obviously put the animal into anything but a stable state. We therefore used an initial 15 - 20 mg. dose, and supplemented as necessary. While a certain amount of respiratory depression occurs with every barbiturate anesthetic, we do not believe it was an important factor in these experiments. Our impressions were confirmed by arterial blood oxygen saturations, which were usually over 90 per cent even during the early, deeper period of anesthesia. As mentioned, if the saturation was below 90 per cent, the experiment was not proceeded with until respiration improved and arterial oxygen saturation rose. In these experiments, oxygen was not administered because it might aggravate CO₂ retention even though raising the arterial saturation. Positive pressure respirators were not used because, unless these are very carefully employed, they cause diminution of the cardiac output due to interference with venous return to the heart. The dose of Amytal necessary for anesthesia was considerably greater than the doses of Nembutal or Pentothal. While Amytal is considerably longer-acting than the other two drugs, its effect was not nearly so profound.

Cardiac Output: As indicated by the mean values in Table II, the 5 mg. supplemental doses of Amytal and Nembutal caused a slight drop in cardiac output, while with Pentothal the mean values for CO I and CO II were identical. However, there was considerable variation from one experiment to another (Fig.1),

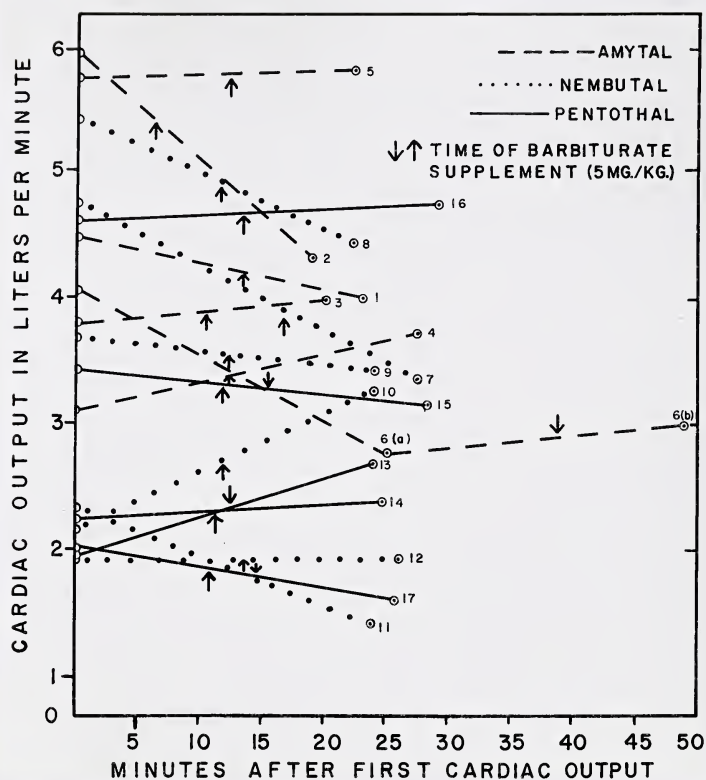


Fig. 1. Change in cardiac output following injection of 5 mg./kg. body weight of barbiturate. Compare with Fig. 2. Numbers indicate number of experiment (Table II).

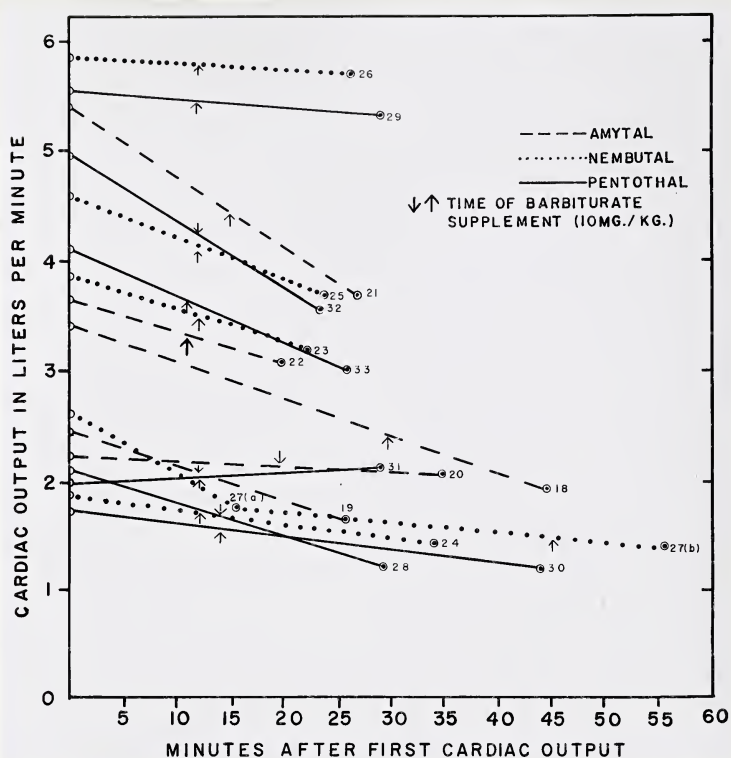


Fig. 2. Change in cardiac output following injection of 10 mg./kg. body weight of barbiturate. In only one of 17 experiments did the output fail to drop. Numbers indicate number of experiment (Table III).

Table IV

Relationship Between Depth of Anesthesia
And Administration of Barbiturate Supplement

"Light" Anesthesia, 5 Mg./Kg. Supplement										"Even" Anesthesia, 5 Mg./Kg. Supplement										"Light" Anesthesia, 10 Mg./Kg. Supplement									
Expt. No.	CO I	CO II	TPR I	TPR II	Expt. No.	CO I	CO II	TPR I	TPR II	Expt. No.	CO I	CO II	TPR I	TPR II															
3	3.86	4.00	2.30	2.15	1	4.50	4.04	2.08	2.29	26	5.85	5.75	1.98	1.99															
5	5.79	5.83	1.31	1.49	2	5.93	4.33	1.35	1.84	29	5.54	5.38	2.14	2.19															
14	2.33	2.39	4.12	4.22	8	5.42	4.46	1.76	2.33	21	5.40	3.75	1.62	2.24															
16	4.67	4.77	2.52	2.62	9	3.72	3.45	2.92	3.20	18	3.44	1.89	2.65	4.57															
4	3.13	3.72	2.76	2.24	17	2.06	1.58	3.96	5.01	24	1.91	1.36	4.68	6.93															
7	4.74	3.37	2.06	2.49	12	2.00	2.01	4.86	4.57	25	4.66	3.71	2.37	2.89															
6(a)	4.10	2.78	2.22	3.02						28	2.11	1.19	4.35	7.46															
15	3.44	3.10	2.37	3.00																									
Mean	4.01	3.74	2.46	2.63		3.94	3.31	2.82	3.21		4.13	3.29	2.83	4.04															
S.D.	1.08	1.12	0.80	0.90		1.66	1.23	1.43	1.31		1.65	1.80	1.20	2.32															

For paired differences

(CO I-CO II),

t=1.043, P>0.3

For (TPR II-TPR I),

t=1.308, P>0.2

(Differences not Significant)

For (CO I - CO II),

t=2.679, P<0.05

For (TPR II-TPR I),

t=2.124, P>0.05

(Excluding Expt. 12, t=3.51,
P<0.02)

For (CO I - CO II),

t=3.61, P<0.02

For (TPR II-TPR I),

t=2.648, P<0.05

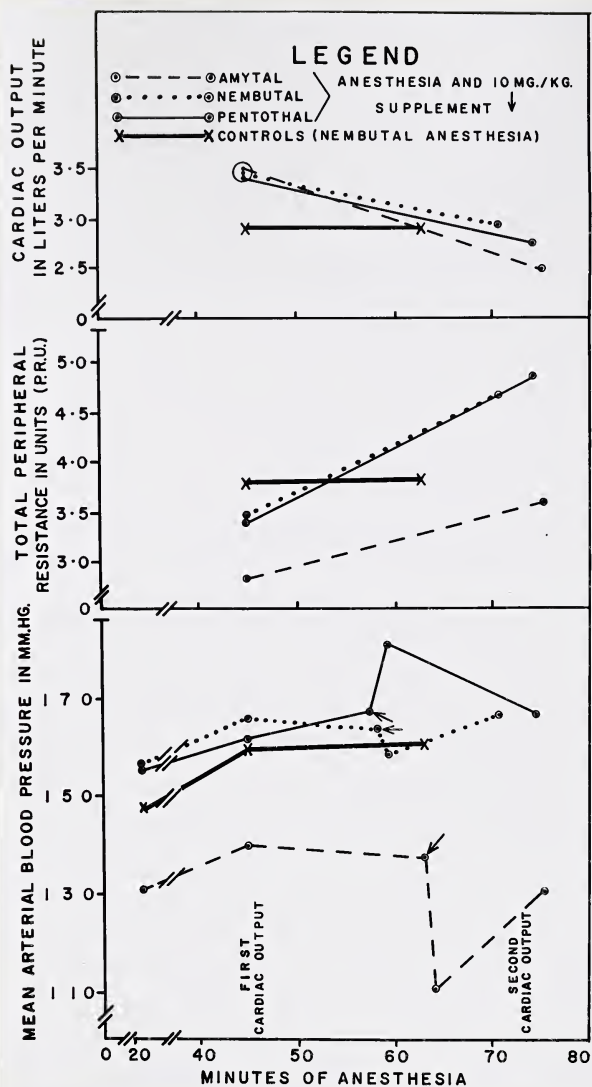


Fig. 3. Changes in cardiac output, peripheral resistance and blood pressure of three groups of dogs receiving 10 mg./kg. supplements of barbiturate, compared with similar determinations in anesthetized dogs receiving no additional barbiturate. Mean values for each group are plotted.

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so the "t" test was applied to the change in output for each dog rather than to the difference between group means. For none of the three groups receiving 5 mg. supplements were the changes statistically significant. Of the 18 sets of determinations, 9 showed an increase in output and 9 a decrease.

On the other hand, the 10 mg. increments of barbiturate caused a fall in cardiac output in each group, averaging 28.4% in the dogs receiving Amytal, 17.2% in the dogs receiving Nembutal, and 19.7% in the Pentothal group (Table III and Fig. 2). For the Amytal group, $P < 0.05$, and approached the 2% level; with Nembutal, $P < 0.01$; with Pentothal, $P < 0.05$. Of the 17 sets of determinations, the cardiac output fell after barbiturate injection in all but one (Experiment 31).

We feel that these results are particularly significant in view of the lightness of anesthesia which we attempted to maintain, and knowing that with the animal very light, no effect might be obtained. To test our figures in another way, we reviewed the protocols for comments regarding the manner in which each dog took the anesthetic, the comments having been made only if this was fairly obvious. The type of anesthesia was classed as "light", "even", or "deep" (there were only two or three of the latter and in these cases we had waited for the animal to become lighter before proceeding). There were 21 such comments of "light" or "even" anesthesia. These examples are listed in Table IV, subdivided into three groups on the basis of "light" or "even", and receiving either 5 or 10 mg. supplements of barbiturate, without regard to which particular barbiturate the dog had been anesthetized with. Of the eight dogs under "light" anesthesia receiving 5 mg. supplements, only three showed a drop in cardiac output while five showed an increase. As might be expected, the "t" test showed that similar findings might occur nearly 40% of the time. However, of the six examples of "even" (i.e. somewhat deeper) anesthesia, also receiving only 5 mg. supplements of barbiturate, five showed

a decrease in cardiac output and the remaining example (Experiment 12) showed virtually no change in output. Application of the "t" test indicated probable significance, with $P < 0.05$. Of seven examples of "light" anesthesia, all showed a decrease in output, and the "t" test indicated that the probability of this happening by chance was only 1 to 2 per cent.

These findings indicate that a 10 mg. supplement of any one of the three barbiturates in question will decrease the cardiac output of anesthetized dogs, regardless of whether anesthesia is light or not. If anesthesia is somewhat deeper ("even" or "moderate"), the chances are better than 20 to 1 that the cardiac output will be diminished by only 5 mg. of barbiturate. If the dog is under "light" anesthesia, however, the 5 mg./kg. supplement may or may not decrease the output; this would appear to depend partly on just how "light" the dog is. The 5 mg./kg. dose would probably not be enough to affect an animal which is virtually awake. Another possibility which might explain the marked drop in output which occurred in some dogs receiving 5 mg. is that the animal might appear to be awakening (e.g. on the basis of more rapid respiration), but if a lag period does exist between a decrease in depth of anesthesia and an increase in cardiac output, during this lag period a 5 mg./kg. supplement of barbiturate would depress the output much more than expected.

Because our experience has not been great with dogs under deep anesthesia (e.g. Experiments 6a and 6b, Table II), and because the literature contains little information on the cardiac output as the depth of anesthesia decreases, two further experiments were performed (Table V). During and following the COI determinations, Dog 29 was obviously awakening from his anesthetic; 1 c.c. of Nembutal (about 2 mg./kg. body weight) was administered without apparent effect. A second set of determinations were taken which showed a 37% increase of CO II over CO I due to lighter anesthesia. The other animal in this table, Dog 30, was anesthetized deeply, the arterial oxygen

Table V

Hemodynamic Measurements In Two Dogs

Under Light (Dog 29) And Very Deep (Dog 30) Anesthesia

Dog Number	Determinations Associated with First Cardiac Output (CO I)						Determinations Associated With Second Cardiac Output (CO II)							
	C.O. I (L./Min.)	Heart Rate Per Minute	R. V.	P.A.	Hem.	T. Pulm. I	T. P. R. I	C.O. II (L./Min.)	Heart Rate Per Minute	R. V.	P. A.	Hem.	T. Pulm. R. II	T. P. R. II
29	2.39	180	21 7 41	18 5 11	183 142 128	0.276	3.56	3.79	195	28 9 -3	20 12 2	193 149 133	0.190	2.36
30	1.88	106	30 10 5	23 14 8	184 139 114	.447	4.44	2.80	140	30 11 1	23 14 6	202 151 129	0.300	3.24

saturation being only 70%. Oxygen was administered to raise the saturation (to 100%) to eliminate baseline fluctuation of the galvanometer. CO I was 1.38 and CO II 2.30 liters per minute, despite no evidence of change in depth of anesthesia. Deep anesthesia is obviously not a solution for maintaining stable circulatory dynamics.

In addition to showing the degree of drop in cardiac output which may occur with 5 and 10 mg./kg. increments of barbiturate, these results also indicate the importance of the time factor. Unless the dog is rather light, a 10 to 15 minute waiting period is not long enough for the depressing effect of the barbiturate injection to have disappeared. From our limited experience in this regard, it would appear that 30 minutes or longer is required. An example is Experiment 35 (Table VII), in which Dog 29 received a 10 mg./kg. supplement of Pentothal and developed a cardiac arrhythmia; this was finally converted 30 minutes after the injection ($42\frac{1}{2}$ minutes after COI). The cardiac output was 2.93 l./min., compared with the previous output of 2.83 l./min. Since Pentothal is ultra-short acting, a longer period than 30 minutes would probably be needed with a 10 mg./kg. dose of Nembutal, and still longer with Amytal.

Arterial Blood Pressure and Total Peripheral Resistance: As indicated by Tables II and III and Fig. 3, the arterial pressures of most dogs, including those of the control group, tended to increase from the initial observation period (30 to 40 minutes) to the time of CO I determinations. This was probably due to recovery from the initial respiratory and circulatory depression accompanying induction of anesthesia. The mean arterial blood pressure remained fairly stable following the CO I determinations. The effect of injection of supplemental barbiturate is indicated by the group averages of mean blood pressure which are plotted in Fig. 3. Injection of Amytal and

Nembutal was usually associated with a drop in blood pressure, the time of onset and acuteness of which varied directly with the speed of injection and size of dose. Following this drop, the pressure in most cases gradually returned to the previous level; sometimes the pressure rose to higher levels (the so-called "overshoot" phenomenon). Occasionally if the barbiturate was injected very slowly, there was no drop in pressure but a slight increase which gradually decreased to the previous level. With Pentothal, a rapid injection produced a blood pressure drop as with the other two barbiturates, but a slow injection (which most of ours were) usually produced a rise in blood pressure, as shown in Fig. 3, which gradually fell.

Total peripheral resistance naturally reflected the decrease in cardiac output and maintenance of blood pressure, rising in all groups. In the 5 mg. groups, these increases amounted to 6% for Amytal, 16% for Nembutal, and 6% for Pentothal, but application of the "t" test showed that these changes could not be considered significant in these numerically small groups of dogs. With the 10 mg./kg. injection, changes were more marked, being 30% with Amytal, 32% with Nembutal, and 38% with Pentothal. Despite the fact that every dog in these three groups showed an increase in resistance, and considering the magnitude of the increase, the results of the "t" test were surprising. Only the Pentothal group was "statistically" significant, the probability value (P) being less than 0.05. The Nembutal group was very close, P having a value of about 0.053. The Amytal group showed P about 0.074 which, statistically, is not "significant", but we feel that a 30% increase in resistance is impressive and unlikely to occur by chance. However, the generally lower blood pressures of dogs in this group suggests that Amytal may differ from the other two barbiturates in its effect on the Peripheral vascular bed.

As was mentioned above, certain experiments were subdivided on the

basis of depth of anesthesia and size of supplemental dose (Table IV). Dogs under "light" anesthesia receiving 10 mg./kg. doses showed a considerable increase in total peripheral resistance ($P < 0.05$). The "light" dogs with 5 mg. supplements showed a slight increase, but P was greater than 0.1. The "even" anesthesia group, receiving 5 mg. supplements of barbiturate, also showed an increase in peripheral resistance, but application of the "t" test yielded a value for P greater than 0.05. We feel that the increase in resistance is nevertheless significant, as would be expected in view of the significant ($P < 0.05$) decrease in cardiac output. Five of the six dogs in this group showed an increase but one showed a small decrease, affecting the group statistically. Since this small decrease in resistance in this dog was accompanied by a slight increase in cardiac output, it may be assumed that the dog was awakening. To evaluate the changes in peripheral resistance in the remainder of the group, recomputation was carried out on the basis of 5 dogs, and yielded $P < 0.02$. While this recomputation may appear somewhat artificial, it does indicate that in the dogs in which depression of output occurred, a significant increase in peripheral resistance also occurred.

Table VI lists findings from experiments in which the cardiac output increased. The percentage increase was 12.7, but the peripheral resistance decreased only 4.7%; this suggests a lag in resistance change behind output change.

Heart Rate: The heart rate increased from the initial to the CO I determinations. Except for a tendency to increase during the blood pressure drop accompanying injection of the supplemental dose, (likely a pressoreceptor reflex effect) the heart rate remained fairly stable throughout the period of observation. There was a tendency for the heart rate to decrease if the cardiac output decreased, and to increase if the output increased (since the

The first part of the paper is devoted to a general discussion of the problem of the existence of solutions of the system of equations (1) for arbitrary values of the parameters α and β . It is shown that the system has solutions for all values of the parameters α and β if the function $f(x)$ is continuous and has a bounded derivative. In the case when the function $f(x)$ is not continuous or has an unbounded derivative, the system may not have solutions. The second part of the paper is devoted to the study of the properties of the solutions of the system (1) for arbitrary values of the parameters α and β . It is shown that the solutions of the system (1) are unique and depend continuously on the parameters α and β . The third part of the paper is devoted to the study of the properties of the solutions of the system (1) for arbitrary values of the parameters α and β . It is shown that the solutions of the system (1) are unique and depend continuously on the parameters α and β .

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Table VI

Comparing Change in Total Peripheral Resistance with Change
in Cardiac Output in Those Dogs Showing Increase in Output.

C.O.I	C.O.II	% Change	T.P.R.I	T.P.R.II	% Change
2.15	2.59	20.5	4.05	3.47	-14.3
3.86	4.00	3.6	2.30	2.15	- 6.5
3.13	3.72	18.8	2.76	2.24	-18.8
5.79	5.83	0.7	1.31	1.49	13.7
2.78	2.98	7.2	3.02	2.94	- 2.6
2.02	2.66	31.6	4.04	3.23	-20.0
2.33	2.39	2.5	4.12	4.22	2.4
4.67	4.77	2.1	2.52	2.62	4.0
2.26	3.31	46.5	3.24	2.85	-12.0
2.00	2.01	0.5	4.86	4.57	- 6.0
2.00	2.12	6.0	4.35	4.73	8.7
Mean 3.00	3.31	12.7	3.32	3.14	- 4.7

Application of t test for paired differences:

(1) For (COII - COI), $t = 3.05$

$P < 0.02$ (significant change)

(2) For (TPRI - TPRII), $t = 1.70$

$P > 0.05$ (nearly 0.1) (No significant change)

Table 1

Summary of results of the experiment on the effect of temperature on the rate of reaction of hydrogen peroxide with potassium iodide.

Temperature (°C)	Time (s)	Volume of gas (cm ³)	Rate of reaction (cm ³ /s)	Reciprocal of rate (s/cm ³)	1/T (K ⁻¹)
10	120	10	0.083	12.0	0.00303
15	90	10	0.111	9.0	0.00315
20	75	10	0.133	7.5	0.00326
25	60	10	0.167	6.0	0.00337
30	50	10	0.200	5.0	0.00349
35	45	10	0.222	4.5	0.00360
40	40	10	0.250	4.0	0.00370
45	35	10	0.286	3.5	0.00381
50	30	10	0.333	3.0	0.00392
55	25	10	0.400	2.5	0.00405
60	20	10	0.500	2.0	0.00417
65	15	10	0.667	1.5	0.00430
70	12	10	0.833	1.2	0.00442

Graph of 1/T vs 1/rate showing a linear relationship.

Equation of the line: $1/rate = 10.5(1/T - 0.00303)$

Activation energy = 50.0 kJ/mol

Prepared by: [Name] Date: [Date]

Checked by: [Name] Date: [Date]

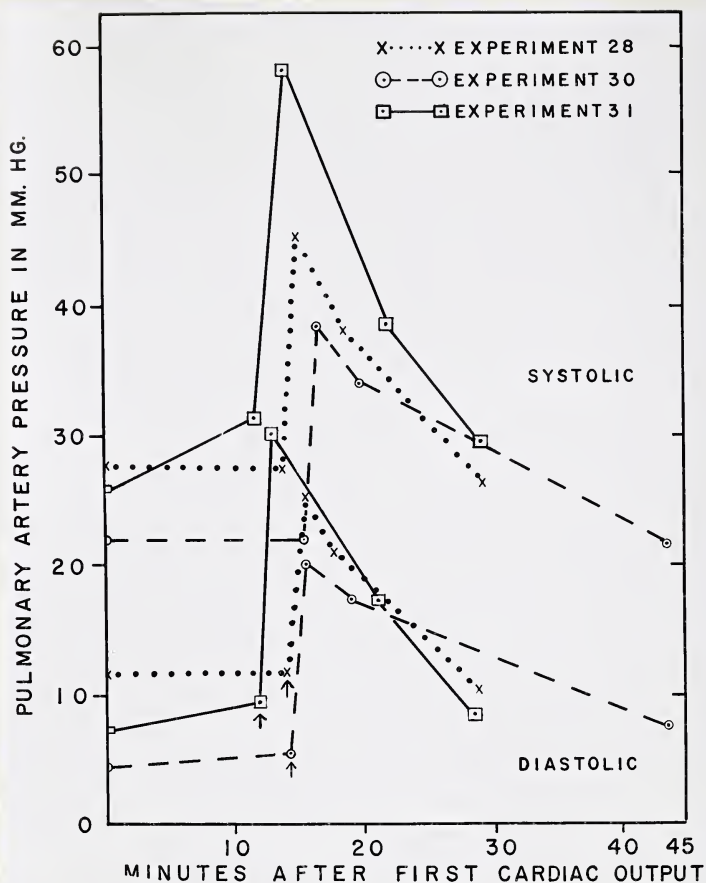


Fig. 4. Showing abrupt increase in pulmonary artery pressure of 3 dogs following injection of 10 mg./kg. supplement of Pentothal. These dogs did not develop cardiac arrhythmia. Arrows indicate time of injection. Last points plotted were measured at the time of the second cardiac output determination.

animal was probably under lighter anesthesia), but sometimes these events were reversed.

End Diastolic Pressure in the Right Ventricle: In about two-thirds of the experiments, injection of the supplemental barbiturate resulted in either no change of the end diastolic pressure or caused a slight decrease, if the cardiac output remained the same or decreased. An increase in output in isolated instances increased the end diastolic pressure slightly. In view of the difficulty of determining whether changes were due to barbiturate, or CO₂ retention etc., and the limitations of the recording apparatus to reflect these slight (1 mm. Hg.) pressure changes, no definite conclusions can be drawn, although we feel that deeper anesthesia probably decreases right ventricular end diastolic pressure slightly.

Pulmonary Artery Pressure: With Amytal and Nembutal, variations in pulmonary artery pressure were inconstant. With Pentothal, however, particularly in the 10 mg. group, there was a marked increase in the PA pressure, frequently amounting to 100% increase (Fig. 4). Unfortunately, pressure pulse recordings to study the mechanism of this rise were not available because the barbiturate was injected through the catheter. The rise occurred by the end of injection, and in view of the rapidity of onset (less than 60 - 90 seconds), it seems unlikely that CO₂ retention due to apnea from this rapid-acting drug can be the only explanation. Perhaps in the dog, the mechanism of this increase in pulmonary artery pressure with Pentothal is similar to that which causes the increase in peripheral arterial pressure. Acute anoxia might also be a factor^{22,23}.

Cardiac Arrhythmia: In six experiments, supplemental injection of Pentothal, particularly in 10 mg./kg. dosage, produced ventricular bigeminy. The hemo-

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dynamic findings are shown in Table VII. Fig. 5 shows the onset of the arrhythmia at a slow-speed recording from Experiment 33. The femoral artery pressure pulse shows gradual diminution in amplitude of pulses from the extrasystolic beats with concomitant increase in pressure from normal beats, until only the normal (major) pulses appear, with the extrasystolic (minor) pulses buried as a hump on the descending limb of the pressure pulse.

Rather than appearing gradually as in this case, the onset of extrasystoles was sometimes abrupt. The "normal" beats delivered tremendous pressures; on one occasion, pressure pulses were 338/150, with a mean of 212 mm. Hg. It has been said that this occurrence of bigeminy ("pseudoalternans") in anesthetized animals is usually associated with high blood pressures and rapid heart rates¹², but in two of our experiments (see Table VII) the phenomenon occurred at rates of 95 and 145 beats per minute.

Since the arrhythmia first occurred in Dogs 25 and 29, both of which had received several anesthetics, it was felt that sensitivity to barbiturates might have been a factor. Dog 30, which had never before received an anesthetic, was chosen for the next experiment, and developed the bigeminy. Almost all the barbiturate injections were made with the catheter tip in the pulmonary artery; an experiment was carried out with the catheter tip withdrawn to the upper superior vena cava, to provide better dilution of the drug solution by the blood and minimize any local effect on the heart. The bigeminy recurred despite this measure.

The greatest duration of the arrhythmia in our first experiences with it was 30 minutes, an unsatisfactory delay at best, and in these experiments unfortunate since such a delay after a supplemental injection of short-acting Pentothal might provide time for recovery of cardiac output depression. This proved to be the case (Table VII, Experiment 35). A conversion mechanism was sought, and since the literature has suggested that the bigeminy is

TABLE VII

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Hemodynamic Measurements In 6 Experiments With
Pentothal Supplementation (10 Mg./Kg.) Showing
Changes Due To Arrhythmia.

Experiment No.	Dog Number	Cardiac Output (COI) in Liters Per Minute	Determinations Associated With First Cardiac Output				Determinations Before Injection of Pentothal				Dose of Pentothal Mg./Kg.	
			Pressures s/d, m				Pressures s/d, m					
			Heart Rate Beats/Min.	Right Ventricle	Pulmonary Artery	Femoral Artery		Heart Rate Beats/min.	Right Ventricle	Pulmonary Artery	Femoral Artery	
15	29	3.44	150	30 -2 9	24 6 14	183 122 136	145		28 7 15	184 120 136	5	
29	25	5.54	210	27 -2 12	27 11 18	271 169 198	210		29 8 18	272 164 200	10	
32	30	4.93	210	35 4 14	34 13 21	178 116 143	210			178 116 143	10	
33	25	4.11	216	30 -1 10	21 9 14	269 172 200	216		21 9 14	269 172 200	10	
34	29	2.54	95	28 0 6	26 6 14	165 103 115	95		26 6 14	165 101 120	5	
35	29	2.83	230	27 -4 11	23 4 14	209 130 160	230	27 -4 11	25 3 14	210 125 158	10	

Determinations During Arrhythmia										Determinations Associated With Second Cardiac Output					
Heart Rate Beats/Min.	Pressures s/d. m									Duration of Arrhythmia	Pressures s/d, m				
	R.V.			P.A.			Fem.				Cardiac Output (COII) in Liters /Min.	Heart Rate Beats/Min.	Right Ventricle	Pulmonary Artery	Femoral Artery
	Major	Minor	Mean	Major	Minor	Mean	Major	Minor	Mean						
210	33 -2	33 -2	14	34 18	34 18	26	236 126	136 112	148	12	310	170	22 -2 9	23 8 16	190 126 150
210	48 0	29 -6	14	43 24	28 14	27	338 216	219 150	212	13	5.38	195	23 -4 8	21 9 15	269 166 196
220	42 10	37 8	20				268 167	173 126	166	x 2	3.48	210	33 2 14	31 14 19	193 130 151
200	50 2	21 -7	10	40 15	20 10	22	315 209	217 154	210	x 10	3.01	195	24 -3 8	23 5 13	253 171 193
180				32 18	30 15	27	212 129	138 115	139	17	*	*	28 -4 11	27 10 18	212 120 152
240	34 -2	37 -3	15	29 8	34 11	21	269 149	155 128	173	x 30	2.93	230	30 -3 13	26 4 16	203 135 162

x Converted (See text).

* Arrhythmia recurred during determination of second cardiac output.

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No.	PUBLISHED WEEKLY				PUBLISHED WEEKLY				No.
	Vol.	No.	Date	Price	Vol.	No.	Date	Price	
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28	1	28	Jul. 9, 1911	10c	1	28	Jul. 9, 1911	10c	28
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64	1	64	Mar. 16, 1912	10c	1	64	Mar. 16, 1912	10c	64
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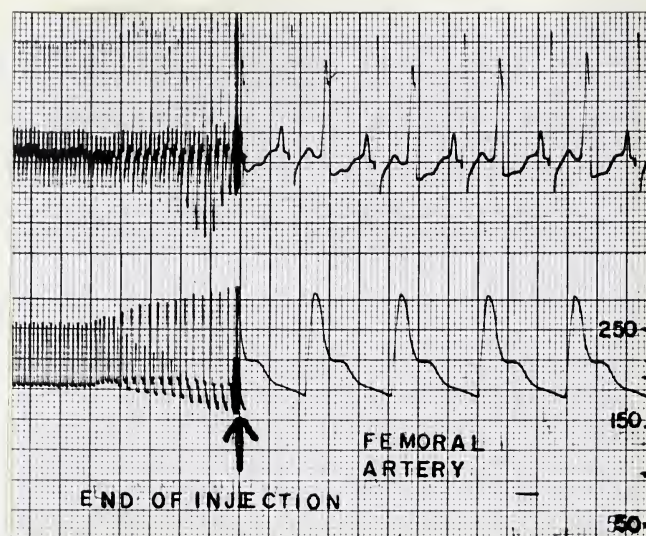


Fig. 5. Development of ventricular bigeminy during injection of 10 mg./kg. of Pentothal, with gradual disappearance of extra-systolic beat until it is visible only as a hump on the descending portion of the arterial pressure pulse curve. Recorder speeds 2.5 and 25 mm./sec. Pressure in mm. Hg. (see Fig. 6).

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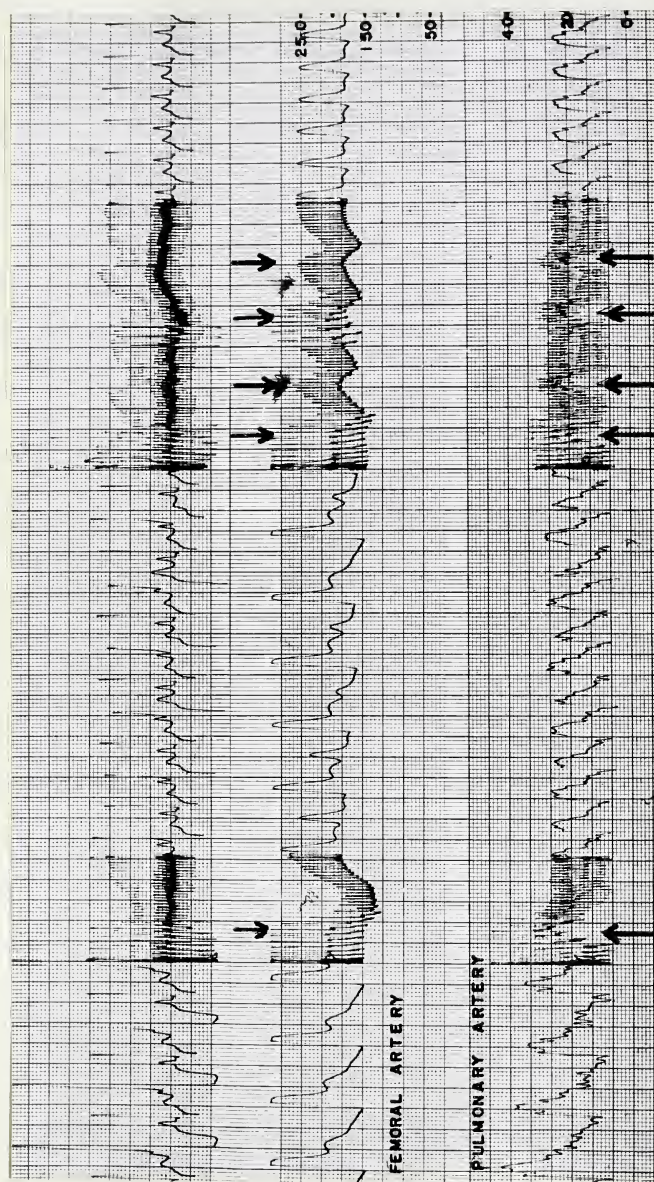


Fig. 6. Recorded a few minutes after Fig. 5. Arrows indicate hyperinflation of lungs with increase in pulmonary artery pressure and decrease in femoral artery pressure, resulting in conversion of the arrhythmia. The arrhythmia recurred twice but was successfully reconverted to normal rhythm. Note that whereas initially only every other beat was visible in the pulmonary artery, after the first conversion every beat was visible, thus differing from the femoral pressure pulse. E.C.G. shows intermittent appearance of P waves before the extrasystoles. Recorder speeds 2.5 and 25 mm./sec. Pressures in mm. Hg.

is due to hemodynamic changes, the lungs of a dog during an episode of the arrhythmia were hyperinflated by blowing into the endotracheal tube. Prompt conversion ensued which, however, sometimes reverted into the arrhythmia. Fig. 6, taken from the same experiment as Fig. 5, shows episodes of conversion and recurrence of the arrhythmia, lung inflation producing the expected changes of increased pulmonary artery pressure and fall in peripheral arterial pressure followed by normal rhythm. It is interesting that the pulmonary pressure pulse (and the right ventricular pulse, not shown in Fig. 6) showed the effects of the bigeminy originally, whereas after the first conversion every heart beat produced small, normal-appearing PA pulses, which persisted even though the bigeminy recurred and produced typical femoral artery pulse changes. In the majority of experiments in which it occurred, the bigeminy produced normal-looking pulses from the right heart rather than the large ("major" -- "minor") pressure pulses as in the femoral artery.

In one experiment, pressure measurements immediately following the cardiac output measurements revealed that the bigeminy had recurred, probably during the cardiac output measurement; the output was increased considerably over the previous output determination (Table VII, Experiment 34).

Curiously, despite the frequency with which we and others¹² have obtained this arrhythmia, some authors have found no E.C.G. abnormalities in anesthetized dogs¹.

DISCUSSION

These experiments indicate that three barbiturates -- Amytal, Nembutal, and Pentothal -- depress the cardiac output of dogs. The degree of depression is roughly the same as that reported in humans^{3,4,17}. The extent of the depression obtained by supplemental injections of these drugs appears to vary with the depth of anesthesia and the size of the dose; thus, a 5 mg./kg. dose administered to a dog under very light anesthesia may have no discernible effect after 12 - 15 minutes, whereas the same quantity given to an animal under deeper anesthesia may profoundly depress the cardiac output. A 10 mg. dose almost always depresses the output.

In view of the fact that myocardial depression by barbiturates has been known for many years^{5,10}, these results are not surprising. However, the situation is far from simple, and the complexity of changes occurring with anesthesia in the living animal may account for some of the varied findings reported in the literature. One must assume that the circulatory system of the barbiturate-anesthetized dog is not necessarily stable, and indeed, is probably stable only if anesthesia is carefully induced and even more carefully maintained. In view of variations in tolerance to barbiturates from animal to animal, and in the same animal at various times and under various conditions, a fixed dose is not advisable. We agree with Nash et al.²⁴ that a dose of 30 mg./kg. for dogs is too great for measurements of physiological parameters.

Under deep anesthesia, respiration is markedly slowed, oxygenation is interfered with, and carbon dioxide retention occurs³². In view of the known circulatory changes which occur with inspiration and expiration³⁷, and which accompany hypoxia^{6,22,23}, it is not surprising that the cardiac output may fluctuate considerably in the deeply anesthetized dog, particularly when measured from minute to minute by a method such as the para-amino hippuric acid constant infusion technique³⁴. Similarly, it is not reasonable to

expect the circulatory system of a dog to remain static when a cardiac output determination is taken at 35 minutes after onset of deep anesthesia and compared with an output determination taken 2 hours and 10 minutes later ³⁴. Somewhere between deep and very light anesthesia, in that broad range classified as "moderate", would appear to be satisfactory for reasonable circulatory stability in dogs. However, no animal can be maintained at a constant depth of anesthesia for considerable time without supplementation of the anesthetizing dose, and it was to determine the effect of such supplements that this project was undertaken.

In addition to what may be termed the "secondary" effects (e.g. CO₂ retention) of barbiturate anesthesia, there are "primary" or direct effects which are less well understood. These include depression of the myocardium ^{5,10}, paralysis of the cardiac vagus nerves ¹⁸, and increased sympathetic activity ¹⁹. In this regard, the papers of Lockett are of interest. Since Nembutal caused no significant change in heart rates of normal atropinized dogs, but slowed the heart in sympathectomized dogs, Lockett suggested that in normal dogs, depression of the cardiac pacemaker by Nembutal is counteracted by augmentation of sympathetic nervous activity ¹⁹. She also found that, while second and third stage Nembutal anesthesia lowered the systolic blood pressure below the sleeping values of well-trained dogs, light Nembutal anesthesia increased the systolic blood pressure ²⁰. Her conclusion was that this rise of pressure might be attributed to stimulation of the sympathetic nervous system. Because the rise was associated with a greater scatter of values than that obtained in her dogs during sleep, she postulated loss of a stabilizing influence on the sympathetic nervous system. This "increased sympathetic activity" is probably due to the vagal blocking which occurs with Amytal and Nembutal. The theory seems to explain at least some of the findings which we and others have observed with barbiturate

anesthesia. It explains the increased mean blood pressure which has been reported with Nembutal. It explains the increase in heart rate which usually occurs with induction of anesthesia. It may explain the finding by Brendel et al.² that the cardiac output during barbiturate anesthesia never fell below the minimal values obtained on resting unanesthetized trained dogs; these authors concluded that the decrease in cardiac output should be regarded as a reduction to a minimal resting output. It may explain the suggestion by Foltz et al.⁵ that Nembutal produces a circulatory state comparable to moderate or exercise levels of activity. It may explain, at least partially, the tachycardia which we have associated as the first sign of lightening anesthesia, and which in our control group occurred without overall change in cardiac output or total peripheral resistance. Increased sympathetic activity would explain the finding that the decrease in cardiac output is associated with a greater increase in peripheral resistance, whereas increase in output is not associated with as great a decrease of peripheral resistance as would be expected.

The suggested lag in cardiac output behind respiratory and other activity which indicates lighter anesthesia may explain the unexpected magnitude of the drop in cardiac output which occurred in some of our dogs. Caution would therefore appear necessary in injecting supplemental doses of barbiturate when the dog's respiratory system is under light anesthesia but the cardiovascular system is not. This may explain why Nash's group²⁴ found a progressive decrease in cardiac output during prolonged Nembutal anesthesia; their dogs were relatively deep, and received average supplementary doses of 2.45 to 4.22 mg./kg. of Nembutal. It seems quite possible that the cardiac output was depressed more than the depth of anesthesia indicated, accounting for the progressive drop in output which these workers observed.

This lag in cardiac output may be due to: (1) Myocardial depression, direct or mediated through medullary centers; (2) An increase in blood pressure greater than decrease in cardiac output; (3) Total peripheral resistance increase (i.e. vasoconstriction) or splanchnic capillary pooling¹⁴ of blood, either one causing decreased venous return to the heart and therefore decreased cardiac output. While our observations are not definite in this regard, we feel that some decrease in right ventricular end-diastolic pressure did occur with anesthetic depression; others have noted decreased central venous pressure³ or intrathoracic blood volume¹⁷ in anesthetized humans.

One or two comments on individual barbiturates should be made. Although Amytal is known to be a vagal blocker¹⁸, the increase in total peripheral resistance in our Amytal dogs was not proportionate to the drop in cardiac output, when compared with the Nembutal and Pentothal groups. Also, the blood pressure levels in the Amytal dogs tended to be lower than in the Nembutal and Pentothal groups. These findings may have been secondary to the greater doses of Amytal required to maintain anesthesia. As far as Pentothal is concerned, we have confirmed Gruber's findings of several years ago¹² that use of this drug not infrequently is associated with ventricular bigeminy in dogs. Gruber found that decreasing the blood pressure converted the rhythm; our method of conversion, that of hyperinflation of the lungs, would appear to act in similar fashion. The association of the arrhythmia with increased blood pressure was confirmed in unusual fashion in two dogs, in which ventricular extrasystoles occurred intermittently for only one to three beats at the peak of Traube-Hering waves. While this ventricular bigeminy appears not to occur in humans, it is of interest that the Mayo group⁴ observed that in one of their group of 13 patients studied under Pentothal anesthesia, the blood pressure suddenly rose from 154/88 to

210/127 and a bigeminal pulse developed as anesthesia was deepened; this disappeared as soon as anesthesia was permitted to return to lighter levels.

The marked increase in pulmonary artery pressure which occurred in some of our dogs during injection of Pentothal does not appear to have been reported previously. The rise in pressure was very rapid; Nahas and L'Allemand²² showed that respiratory arrest rapidly increases P.A. pressure and some of our dogs were apneic and therefore hypoxic for a time after 10 mg. of Pentothal. A direct effect of the drug on the pulmonary vascular bed does not seem probable, even though most of our injections were made with the catheter tip in the pulmonary artery, except for one case, in which a 2% solution was injected very slowly into the upper superior vena cava, and increased the P.A. pressure. In this regard a recent paper has reported two cases of primary pulmonary hypertension in which death occurred following Pentothal and secobarbital injection. The authors suggested possible decrease in cardiac output in these two patients, as causing death, but it is possible that barbiturate aggravation of pulmonary hypertension may have been the important factor.

The progressive increase in cardiac output, accompanied by decreased total peripheral resistance, reported by Greisheimer's group for dogs anesthetized with Pentothal and other short-acting barbiturates appears to be due to lighter anesthesia regardless of blood concentration of barbiturate ("acute tolerance"²⁸ might be a factor). Also, the findings might be influenced by the considerable quantities (300-400 c.c.) of saline injected into the dogs over a 40 to 80 minute period. The authors suggestion that dogs' cardiac output is increased by Pentothal anesthesia is unwarranted.

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CHAPTER II

1. The first principle of the theory of the mind is that the mind is a faculty of knowledge, and that knowledge is a faculty of the mind. This is the first principle of the theory of the mind, and it is the first principle of the theory of the mind.
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INTRODUCTION

Since the extensive studies by Emile Holman, contributions to the literature have appeared from time to time on the subject of arteriovenous fistula, but in virtually none is the relationship of the myocardium to onset of the heart failure ("high output heart failure") which may occur with A-V fistula discussed in any detail. Thus, Youmans' review of the mechanism of high output circulatory failure concludes: "Whether there is also a cardiac weakness factor remains to be demonstrated in individual cases". Some reports of experimental A-V fistula in animals mention ^{4,13} pulmonary edema (left ventricular failure) as the cause of death, but ascites and peripheral edema (presumably due to right heart failure) may also be present in these animals. Since, in the presence of an arteriovenous fistula, both sides of the heart must increase their work, it was felt of interest to determine whether the left and right ventricles fail simultaneously, or whether the left ventricle fails first and the right ventricle secondarily.

The opening of an arteriovenous shunt causes numerous important circulatory changes, ^{25,45} which may be divided into two phases: (a) those occurring immediately upon opening of the shunt, and (b) the delayed effects of the shunt. We will also briefly consider: (c) the changes which occur immediately after closure of the shunt, and (d) the delayed effects of closure.

(a) Immediate effects of arteriovenous shunt. The opening of a large arteriovenous communication may cause immediate death from circulatory failure, but the changes due to opening a fistula of moderate size include:

1. A fall in general arterial blood pressure affecting both diastolic and systolic levels.
2. An increase in pulse rate.
3. An increase in the cardiac output.
4. An increase in the pressure in the involved vein, proximal and distal to the fistula.

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5. A decrease in the size of the heart.
6. To this original list of Holman's may be added the observation, made by some investigators, that the central venous pressure or right atrial pressure is not increased or may decrease slightly. Another group has reported an "insignificant" increase in right atrial pressure upon opening an A-V fistula.
7. A slight increase in pulmonary artery pressure.

(b) Delayed effects of arteriovenous shunt. The delayed effects of an A-V fistula on the circulation are tabulated next, to permit discussion of the progression of changes which occur.

1. An increase in blood volume of a degree which is roughly correlated with the size of fistula.
2. Elevation of the venous pressure to levels well above the normal range.
3. Enlargement of the heart, due mainly to dilatation and only to a minor degree to hypertrophy.
4. A recovery from the lowered blood pressure which occurs immediately after formation of the fistula, the systolic being equal or higher, the diastolic definitely lower, than existing before the formation of the fistula, thus producing a greatly increased pulse pressure, although mean arterial pressure returns to pre-operative levels.
5. The heart rate continues to be increased.
6. The cardiac output remains elevated and, in fact, increases over the immediate post-operative value.

To consider the progression of changes, the opening of an A-V fistula results in the animal bleeding into the involved venous bed. While in one respect the situation is akin to hemorrhage, it is also analagous to

obstruction of venous return from an extremity with a cuff inflated to a pressure of 60 - 70 mm. Hg. These two analogies explain the fall in arterial blood pressure and the increase in pressure in the involved vein which may be sufficient to cause marked local ~~tiss~~oedema. The relative stasis in the involved venous bed decreases the circulating blood volume, while the bleeding from artery into vein decreases the effective arterial blood volume. The decrease in size of the heart is partially due to the reduction in blood volume, but more so to more complete emptying of the heart as a result of the decreased arterial pressure which, reflexly through the sino-aortic pressoreceptor reflexes, causes stimulation of the heart through its sympathetic nerves: the heart rate occurs and cardiac output is increased. The slight increase in pulmonary artery pressure is probably due to this increased output. At the same time, the fall in arterial pressure reflexly causes peripheral vasoconstriction; there is decreased blood flow to the rest of the body tissues and the arteriovenous oxygen difference increases (as much as 20%). The increase in cardiac output is therefore not sufficient to supply the tissues with the same amount of blood which they received pre-operatively. The central venous or right atrial pressure remains the same or falls, despite the increased flow of blood through the shunt into the venous system; this is partially due to reduction in circulating blood volume, and partially to the reflex vasoconstriction of the arterial bed. It is interesting that in one dog reported by Van Loo and Heringman, the formation of a femoro-femoral fistula did not increase the total blood flow in the inferior vena cava, so great was the decrease in venous return from the tissues as a result of their decreased blood supply.

Following these immediate effects of creating an A-V fistula, the most important change which occurs is an increase in the blood volume and in the interstitial fluid space. This blood volume increase, proportional to the size of shunt, results in recovery of mean blood pressure (although the

pulse pressure naturally remains increased), further elevation of cardiac output, elevation of venous pressure, and enlargement of the heart. The heart rate remains faster than before opening of the fistula, although it may slow from the initial increase. Vasoconstriction is not a part of the picture of chronic arteriovenous shunt, unless heart failure, and therefore a decrease in cardiac output, supervenes. It has been reported that some further decrease in peripheral resistance occurs, as a result of development of collateral circulation about the fistula site.^{4, 25} Regarding the decrease in heart size and fall in central venous pressure mentioned above, the Minneapolis group⁴ has reported that these may return to normal within hours after creation of the fistula; they increase still more with time, as the blood volume increases. The pulmonary artery pressure may show a considerable increase. Gibbon and Churchill¹⁷ found in cats a small but invariable immediate increase (5 - 12%) in P.A. pressure with a single acute femoral arteriovenous shunt, with any accompanying increase in cardiac output of 24 - 59%. Van Lood and Heringman⁴³ also reported small increases with similar shunts. Lillehei et al.³⁰, in chronic preparations with larger shunts, obtained average P.A. pressure increases of 92%, accompanying an average cardiac output increase of 172%. They deduced a decreased pulmonary vascular resistance due to mechanical distention of the lung vessels, the increase in P.A. pressure being due to the increase in cardiac output.

The increase in blood volume, which the Minneapolis group³⁰ found to average 37% in one series of dogs, appears to be renal in origin, although the exact mechanisms are as yet unknown. Thus, experimental fistulae cause renal retention of salt and water. Hilton et al.²⁴ also reported a decrease in renal plasma flow and a slight decrease in glomerular filtration rate, while Epstein et al.¹¹, in humans with A-V fistulas, found renal blood flow and glomerular filtration rate to be unchanged when the fistulas were closed

(manual compression) or released. However, compression of the fistulas in these patients increased renal excretion of sodium 144% over the values obtained when the fistulas were released. Renal excretion of potassium was not altered in any consistent fashion with compression or release of the fistula. There was, incidentally, no increase of renal vein pressure in these patients, some of whom had femoral arteriovenous fistulas.

Since, as will be mentioned, compression of a fistula results in considerable increase of arterial pressure, the maintenance at unchanged levels of renal blood flow and glomerular filtration rate in these patients indicates an increase in renal vascular resistance (due to afferent arteriolar constriction) with the increased arterial pressure, yet sodium excretion by the renal tubules was augmented. In view of the sodium retention which occurs with opening of a fistula, Epstein et al.¹¹ have hypothesized that renal excretion or retention of sodium is conditioned by the degree of filling of some portion of the arterial tree. These renal hemodynamic (and excretory) changes occur, despite the fact that compression of a fistula results in rapid active vasodilatation of other portions of the vascular tree.

(c) Immediate effects of closing shunt.

1. A sharp rise in blood pressure, particularly the diastolic pressure, and a decrease in heart rate.
2. An increased heart size.
3. An increase, and then a fairly rapid decrease, in central venous pressure.
4. A decrease in pulmonary artery pressure.
5. A decrease in cardiac output.

Closure of the fistula decreases the run-off of blood from the arterial tree, raising the total peripheral resistance and therefore the

blood pressure. This increase is most marked in the diastolic pressure; the pulse pressure is thus narrowed and the mean arterial pressure raised. There is then a reflex slowing of the heart rate. The greater than normal blood volume results in an increase in central venous pressure and an increased heart size; the latter may cause death in an already weakened heart ⁴⁵.

These effects are partially compensated for by dilatation of the arterial tree, as noted by Van Loo and Heringman ⁴³, although this increase in arterial volume cannot compensate for the great increase in blood volume which occurs with chronic fistulas. The decrease in cardiac output results in a decrease in pulmonary artery pressure. The decrease in cardiac output is due to:

(a) reflex slowing of the heart rate, (b) an increase in arterial pressure against which the ventricle must develop its load (this presumably contributes to the increase in heart size), and (c) a reduction in the input load as a result of closure of the shunt.

(d) Delayed effects of closure of the shunt.

1. A gradual readjustment of the blood pressure to the level present before opening of the fistula.
2. Gradual return of heart rate to normal.
3. Decrease in total blood volume.
4. Decrease in size of the heart.

The operative mechanism involved, as indicated previously, is the increased excretion of sodium.

This review of the pertinent literature indicates that the principal hemodynamic factor producing the many changes consequent to the opening of an arteriovenous shunt is the alteration in effective blood volume. The "congestion" in high output circulatory failure thus appears to be compensatory in nature, the degree of compensation varying, roughly, with the size of shunt. Less is known about the part played by the myocardium of the left and

right heart when failure supervenes in the presence of an arteriovenous shunt. It would appear that the failure is "congestive" in type rather than myocardial. It is agreed that when failure does occur, there is usually some decrease in the cardiac output, but the output remains elevated above normal levels. Thus, while failing, the heart is performing considerably more work than the heart in so-called "low output" failure, when the output is within normal range or decreased. Despite this ability to perform more work than normal, the heart in high output failure is, of course, not competent to meet the requirements of the body tissues.

It was to investigate some of the mechanisms of this type of heart failure that the following experiments were performed.

METHODS

The majority of methods employed have been described under Part I of this thesis. Fig. 7 is an example of a dye dilution cardiac output curve, with a moderately high recirculation limb. Fig. 8 shows the calibration curve and tracing of the curve from Fig. 7 on ordinary lined graph paper. The descending limb of the curve was extrapolated through two cycles of semi-logarithmic paper; this extrapolation indicates the shape of the curve had recirculation not occurred and the dye gradually disappeared from the arterial sampling site. The traced original curve has been replotted on the right of Fig. 8 from the calibration curve, since the latter is not linear as explained previously. On this replotted curve is also plotted the result of the semi-logarithmic extrapolation, so that the descending limb of the dye curve gradually approaches zero.

The reason for the previous experiments with barbiturates (Part I) is illustrated by Fig. 9. This animal (Dog 22) was in early heart failure; only 8 mg./kg. body weight of Nembutal was injected into the venous circulation while the left ventricular pressure pulse was recorded, yet considerable

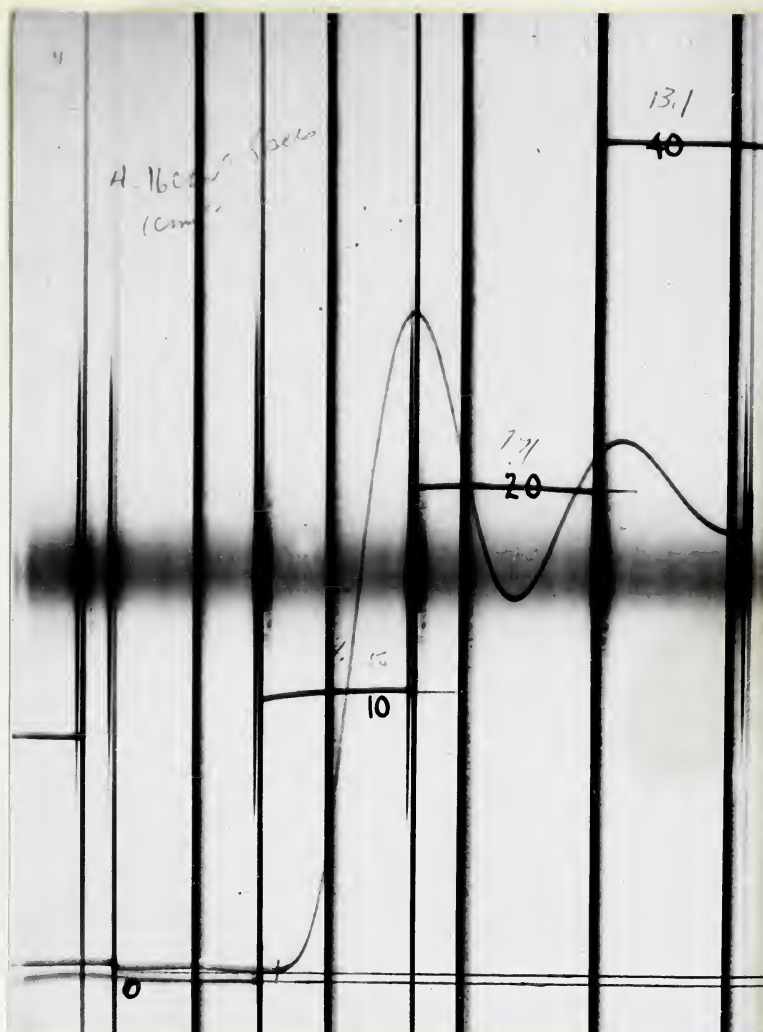


Fig. 7. Dye output curve from dog with A-V fistula, showing rapid recirculation of dye. Horizontal lines with numbers are calibration points. Heavy vertical lines are time marker lines (see text).

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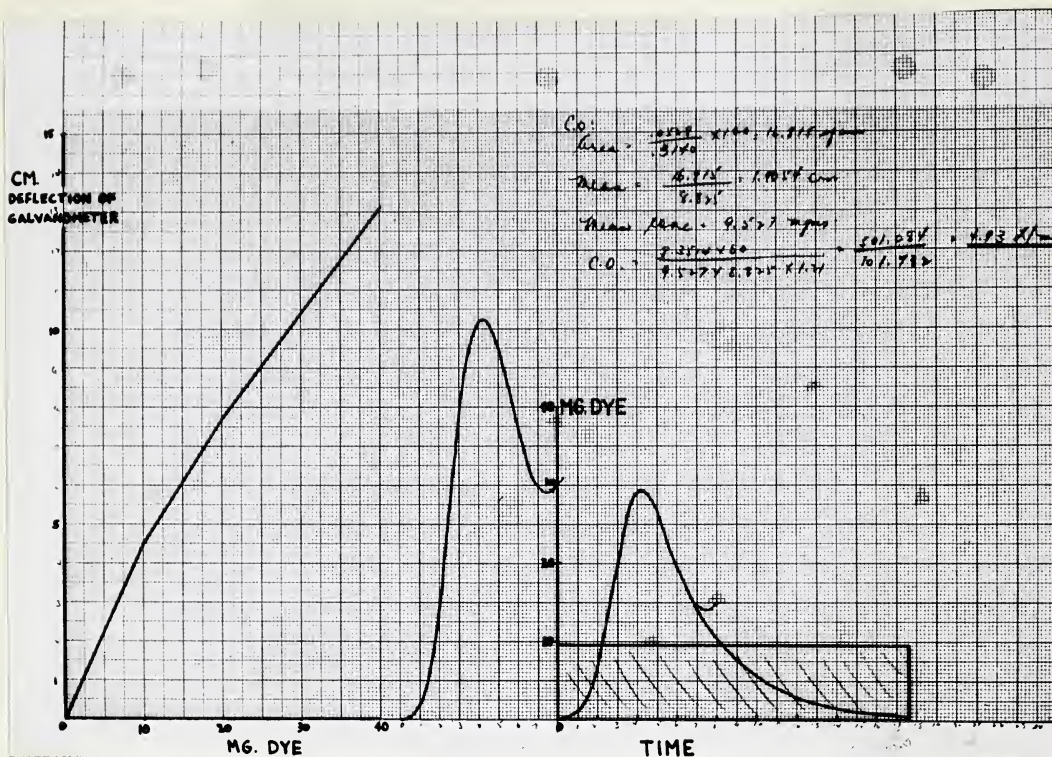


Fig. 8. Calibration curve on left, tracing of dye output curve (Fig. 7) in center, replotted curve on right. Latter curve has been replotted on semilog paper to obtain the descending limb below the point of recirculation. Upper border of the rectangle represents mean concentration of dye during time of the output curve. From time lines in Fig. 7, 1 cm. on the graph represents 1.21 seconds.

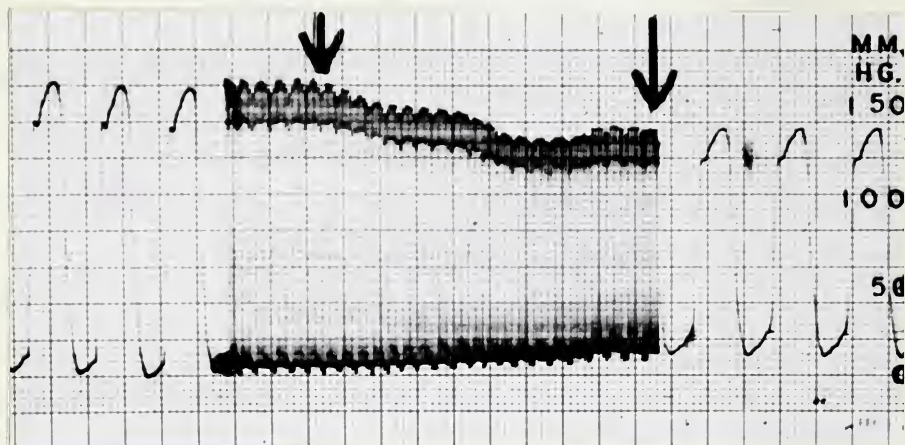


Fig. 9. Effect of intravenous injection of Nembutal, 8 mg./kg. body weight, on left ventricular pressure pulse of Dog 22, in early heart failure. Arrows indicate beginning and end of injection. Note decrease in systolic pressure and increase in diastolic pressure. Recorder speeds 1 and 25 mm./sec.

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changes in systolic and diastolic pressures were produced. For this reason, virtually all experiments in this project were carried out under very light anesthesia, to minimize cardiac depression.

The dogs in this series were prepared two weeks to three months previously. Two operative procedures were carried out: (a) the left common carotid artery was delivered under surgical anesthesia through an antero-lateral incision in the neck, the vagus nerve was carefully dissected free and replaced beside the internal jugular vein, and the artery was enclosed in a loosely sutured skin tube ("carotid loop"). The morbidity from this procedure was moderately high, considerable edema tending to develop in the skin tube about the fourth post-operative day which sometimes progressed to circulatory insufficiency and sloughing. In this series, one dog was used in which this occurred; the artery was tied, necrotic tissue removed, the wound closed, and subsequently the right carotid was transplanted successfully into a skin tube. (b) At the time the carotid loop was formed, thoracotomy was also carried out, the fifth and sometimes sixth ribs on the left side being removed, and the apex of the heart sutured to the chest wall with two or three size 3-0 monofilament nylon sutures. Two dogs fibrillated during ventricular suturing; one died, while the other was successfully defibrillated with an electrical defibrillator. Adequate oxygenation of the animals during surgery obviated this difficulty. SR penicillin 400,000 or penicillin-dihydrostreptomycin 2 c.c. were administered by intramuscular injection for one to three days post-operatively.

After at least two weeks for recovery, the dogs were catheterized and cardiac outputs performed one to three times for baseline (prefistula) determinations. Two animals (Dogs 15 and 18) were kept for three months after carotid transplant and cardiopexy to ensure that these procedures did not cause abnormalities of hemodynamic parameters.

In addition to right heart and carotid artery pressure pulse recording, and cardiac output determination, left ventricular punctures were performed in these dogs. The plastic tubing was disconnected from the intra-arterial needle and a sterile 21-gauge needle was attached. Heparinized saline under pressure was used to fill these and keep them free of air bubbles. The skin of the left thorax was cleansed with iodine, and the needle inserted through the chest wall into the left ventricle. Simultaneous recording was then carried out of right and left ventricular pressure pulses, and the needle withdrawn. Blood volume determinations were also made, using the cuvette oximeter; readings were taken at either 10 minutes, or at 10, 20 and 30 minutes for extrapolation to zero time. Unfortunately this method proved unreliable, gross variations occurring at times.

Following baseline determinations, the dogs were re-operated upon. A transverse, subumbilical muscle-splitting incision was made, the abdominal viscera were displaced and covered with saline-soaked sponges, and the inferior vena cava and abdominal aorta dissected free for two or three inches above the aortic trifurcation. The adventitia was carefully stripped from the aorta. The aorta and vena cava were then brought up into a Smith-Freeman arterial clamp which was tightened down to leave a portion of each vessel in continuity behind the clamp. Parallel incisions were made in each vessel, and continuous 5-0 and 6-0 arterial silk on an atraumatic needle used to form a side to side anastomosis 4 to 13 mm. in length, the continuous suture being tied to stay sutures which were placed at the upper and lower ends of the parallel incisions. On release of the clamp, some bleeding occurred but with slight pressure this subsided in a few moments. The abdomen was closed with plain catgut and interrupted chromic or cotton sutures. SR penicillin or penicillin-dihydrostreptomycin was injected intramuscularly.

Further measurements of the various hemodynamic parameters were

made within one to three days post-operatively on most dogs. One dog died in circulatory collapse despite blood transfusion on the first day and is not reported. Following each experiment, the dogs were given antibiotics; our procedures were clean but not sterile. On days when complete experiments were not performed, left ventricular punctures were done under light Nembutal anesthesia to follow the ventricular pressure changes from day to day.

Catheterization of the right heart was not carried out every day unless it was felt to be essential, i.e., because it was suspected that failure was supervening and pressures were changing; this was to preserve the external jugular veins. In only one dog (Dog 22) did both jugular veins thrombose; in this case, the final catheterizations were performed through the femoral veins.

The order of each experiment was: anesthetization of the dog; placing of the dog on its back with the neck extended; adjustment of the balance bottle to the level of the right atrium (once determined, this level was constant for each dog, measured by rule); balancing of the strain gauges; jugular puncture and insertion of catheter; insertion of needle into carotid artery; determination of oxygen saturations; recording of right heart and carotid pressure pulses; recording of electrocardiogram (leads I, II, III, AVR, AVL, AVF); repeat tracings of pressure pulses; removal of blood (22 c.c) for calibration curve and hematocrit determination; addition of dye to 5 c.c. aliquots of blood and withdrawal of dye through cuvette oximeter, recording calibration curve galvanometer deflections; repeat tracings of pressure pulses; injection of dye from calibrated syringe and recording of dye output curve; setting of clock for 10 minutes for blood volume determination; recording of carotid, pulmonary artery, right ventricle, right auricle and (usually) superior vena cava pressure pulses, with electrical integration of mean pressures; withdrawal of arterial blood through the cuvette oximeter for blood

volume recording; left ventricular puncture and simultaneous recording of L.V. and R.V. pressure pulses; recording of carotid artery and the right heart pressure pulses; occasionally, further withdrawal of blood for 20 and 30 minute blood volume samples; recording of pressure pulses; calibration of the strain gauges against a mercury manometer; injection of penicillin; removal of dog and dismantling of equipment. It can be seen that pressure pulses were recorded at frequent intervals, beginning almost as soon as the indwelling needles and catheter were inserted. The electrocardiogram (lead I or II) was almost always recorded simultaneously with each set of pressure pulse recordings. Checks of balance and zero line of the strain gauges recorder channels was carried out at frequent intervals during the procedure.

All dogs were fed the laboratory dog meal, which provided a well-balanced diet. Because some animals lost their appetites post-operatively, 8 ounces of canned dog meat were added to the diet, daily or every other day, as enticement.

All dogs were autopsied; histological sections of tissues from most of the animals were also studied.

RESULTS

The results of 108 sets of determinations on eight dogs are reported in the accompanying tables and charts. A further 28 experiments were performed on two dogs with aorto-caval fistulas of more than one year's duration, on which iliac arteriovenous fistulas were also created, but since these animals failed to demonstrate any conclusive changes, they will not be discussed.

On the 8 dogs, three lived less than one week after the fistula was created; one lived nearly two weeks but developed an abdominal compli-

cation which provided opportunity for interesting observations; two dogs lived more than three weeks; and two dogs lived more than three months after creation of aorto-caval fistula. This distribution was partially fortuitous and partially due to creation of smaller fistulas as the experiment progressed so that longer term effects might be observed. We found, as others have¹³, that it is difficult to determine how an individual dog will react to the creation of an A-V shunt. Older dogs do not seem to tolerate fistulas of the same size as younger dogs³.

Since the main purpose of this experiment was to determine the extent of ventricular changes in high output failure, these results will be dealt with first. It should be mentioned that our criterion for failure was elevation of the end diastolic pressure in the ventricles. It seems to be generally agreed that dilatation of the heart (i.e., increased volume) is a better indicator of failure than end diastolic pressure²⁸, being an earlier compensatory mechanism, increased length of the myocardial fibers being required for the heart to continue its work at normal levels. This is in accordance with Starling's law of the heart, that "the mechanical energy set free on passage from the resting to the contracted state depends on the area of 'chemically active surfaces', i.e., on the length of the muscle fibres."³⁷ It is unfortunate as far as physiological measurements are concerned that there may be little or no change in the end diastolic pressure with rather large changes in end diastolic volume²⁸. However, to view the problem another way, as long as the heart has compensated by dilatation, without increase in end diastolic pressure, it is not in uncompensated failure. When the myocardium can no longer stretch without elevation in end diastolic pressure, it is then in more severe failure, and estimation of time of failure by measurement of pressure discovers the failure somewhat late, rather than too early. A statement by Sarnoff and Berglund³⁸ is

pertinent, that "much of this debate is artificial. For in any hollow viscus an increase in its volume is accompanied by an increase in pressure and these interdependent variables bear a constant relationship to each other unless a change in elasticity or tone occurs. We consider myocardial failure to be an alteration of the contractility of the myocardial fibers resulting in a shift of the ventricle from a normal function curve to a depressed one. The increased filling pressures are thus not a cause of failure but a consequence of decreased myocardial contractility".

Since it has been repeatedly observed that opening an A-V shunt results in fairly rapid cardiac dilatation ⁴⁵, we feel that measurement of end diastolic pressure is a more logical criterion for failure than measurement of volume increase.

We also realize the difficulties which may occur in attempting to make such measurements from pressure pulses transmitted via cardiac catheters ⁴⁴. Several measures were taken to obtain as satisfactory recordings as possible. An adjustable stopcock readily permitted adjustment of degree of damping. Position of the catheter tip was changed whenever necessary to improve quality of recordings. Recordings were carried out at frequent intervals from the beginning of the procedure, when anesthesia was deeper and heart rate slower, to the end of each experiment when anesthesia was lighter and heart rate faster. Recordings were carried out at two speeds, 25 and 50 mm./sec. All tracings were studied throughout their length, to estimate the end diastolic pressure for that particular experiment. In this regard, it might be mentioned that not infrequently, as failure supervened, early in an experiment when anesthesia was deeper (and barbiturate depression of the myocardium presumably greater) and heart rate slower with consequent longer diastolic filling, end diastolic pressure would be higher than later in the experiment. In these cases, the end diastolic pressure later in the

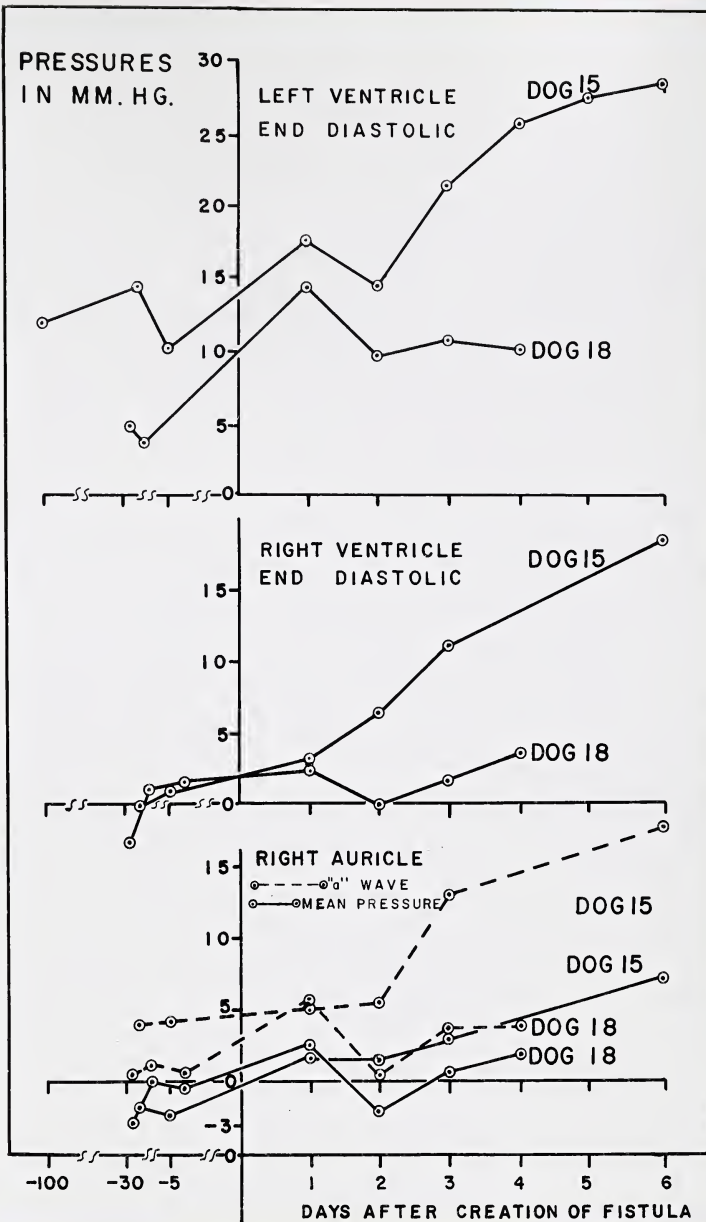


Fig. 10. Changes in intracardiac pressures after creation of A-V fistula in two dogs surviving one week. Note parallel among L.V., R.V. and R.A. pressures. Dog 15, 12 kg., fistula 6 mm. in length. Dog 18, 14 kg., fistula 8 mm. in length.

Table IX

Dog 15: Hemodynamic Changes After Creation of A-V Fistula

Days	Weight in kg.	Nembutal mg./kg.	Oxygen Saturation %			Pressures in mm. Hg.						Heart Rate	Hematocrit	Cardiac Output	Resistance in Units	
			S.V.C.	R.V.	Carotid	R.A. "a" Wave	R.A. Mean	R.V.	P.A.	Carotid	L.V.				Pulmonary	Peripheral
-69	13	—	—	—	96	—	—	20 0	—	147 97	130 12	57	—	1.18	—	5.64
-26	12.4	25.4	—	66	91	4.0	-0.7	32 0	—	194 106	167 14.5	82	45	1.43	—	5.82
-5	11.5	26.1	—	75	99	4.2	-1.0	25 0.8	17 5	135 111	142 10.2	65	40	1.55	.426	4.72
0	Aorto-caval fistula created 6 mm. in length															
1	11.9	21.0	—	—	—	5.2	1.7	44 3.2	36 12	155 65	157 17.8	77	—	—	—	—
2	11.8	20.3	56	83	96	5.4	1.4	48 6.5	36 15	154 53	137 14.8	61	39	2.29	.681	2.52
3	11.5	17.4	39	80	94	13.0	3.1	48 11	41 8	139 41	136 21.5	61	32	1.89	.825	2.82
4	11.4	13.2	—	—	—	—	—	—	—	—	136 26.0	61	—	—	—	—
5	11.4	8.8	—	—	—	—	—	—	—	—	132 27.7	56	—	—	—	—
6.	11.1	19.4	50	84	97	18.0	7.4	68 18.4	54 18	142 34	133 28.6	57	27	3.34	.593	1.47
8	10.8	Died														

* Femoral Artery

Table X
Dog 18: Hemodynamic Changes After Creation of A-V Fistula

Days	Weight in kg.	Nembutel mg./kg.	Oxygen Saturation %			Pressures in Mm. Hg.								Heart Rate	Hematocrit	Cardiac Output	Resistance in Units		
			S.V.C.	R.V.	Carotid	R.A. "a" Wave	R.A. Mean	R.V.	P.A.	Carotid	L.V.								
												Pulmonary	Peripheral						
-29	13.3	30.1	92	77	98	0.4	-3.2	36 -2.6	14	30 14	22	163 134	171 4.7	90	210	50	3.96	.333	2.24
-20	14.9	25.5	88	81	99	1.0	0	37 1.0	10	34 10	20	167 130	170 3.9	74	180	43	3.87	.310	2.29
-2	14.6	29.1	93	85	98	0.4	-0.6	41 1.5	16	—	—	170 125	—	—	200	47	4.74	—	1.78
0	Aorto-caval fistula created 8 mm. in length																		
1	14.6	27.4	85	96	—	5.6	2.7	45 2.4	18	37 16	24	—	177 14.8	85	180	—	—	—	—
2	14.5	31.5	92	* 96	101	0.4	-2.0	47 0	20	33 16	24	167 102	169 9.7	87	196	32	5.244	.275	1.46
3	15.1	39.7	—	—	—	3.6	0.4	45 1.7	18	36 17	25	—	163 10.8	84	180	—	—	—	—
4	14.8	21.3	—	—	—	3.8	1.8	33 3.6	14	27 14	21	—	113 10.1	57	150	—	—	—	—
5	14.7	Died following injection of nembutal 26 mg./kg.																	

* Pulmonary Artery

experiment, at the time of cardiac output, was used for calculation, since it was noted that the barbiturate depression anticipated events, the pressure at a late period in an experiment several days later being equal to the pressure noted early in a previous experiment. In a way, barbiturate anesthesia was something of a "test of failure" of the myocardium.

Dogs which survived less than one week. These included Dogs 13, 15 and 18 (Tables VIII, IX, X, Figure 10). The results for Dog 13 are not charted in Fig. 10, because only one post-operative determination was obtained before the animal died. This revealed a marked increase in right and left ventricular end diastolic pressures and right atrial mean pressure, with a very high (27.3 mm. Hg.) atrial systolic pressure. This dog therefore died in combined left and right heart failure. At autopsy, there was marked edema of the legs. All chambers of the heart were dilated. A few pericardial adhesions were present as a result of the cardiopexy operation, but there was no appreciable degree of myocardial fibrosis at the site of suturing even in microscopic sections of heart muscle. The liver was enlarged, and histologically showed marked central lobular congestion with atrophy of liver cell cords. The spleen was also congested, as were the kidneys. The peritoneal cavity contained a slight amount of ascitic fluid. The lungs, however, showed only slight to moderate congestion. These findings suggest that this animal died with right ventricular failure more severe than the left. Incidentally, the fistula from this dog was the only one in this series which showed fibrinous deposits along its margins, indicating that if the animal had survived, there would have been some diminution in size of the fistula. There was no evidence of bacterial infection on histological examination.

Dog 15 (Fig. 10), an older dog, showed progressive, simultaneous failure of both sides of the heart, beginning on the first post-operative

day. Terminally, end diastolic pressure in both ventricles reached high levels. Right atrial mean pressure followed the increase in right ventricular pressure, but did not rise nearly as sharply. At autopsy, this dog showed evidence of severe failure of both ventricles. The trachea was filled with an abundant quantity of pink, frothy edema fluid, and the lungs were markedly congested; microscopically, erythrocytes within alveoli were numerous, and actual foci of hemorrhage due to capillary rupture were present. In addition to this evidence of left ventricular failure, there was some ascitic fluid in the abdomen, the spleen was very congested, and the liver was enlarged with marked centrilobular congestion and atrophy, with some central hemorrhages and foci of cell necrosis. These findings indicate severe right ventricular failure. The heart showed some apical fibrosis due to cardiopexy suturing (sutures were placed more deeply in this case than in any of the other dogs), and also indicated that left ventricular puncture may have sequelae: occasional small (1.0 - 1.5) yellow areas of recent infarction were present in the anterior papillary muscle and adjacent anterior left ventricle wall. Microscopically, these showed necrotic muscle and infiltration by leukocytes. It is unlikely that these few small areas of muscle damage influenced the course of failure in this dog. It would be interesting to know if failure, with metabolic damage to myocardial fibers, makes the muscle more susceptible to trauma from needle passage.

Dog 18 showed a somewhat different course of failure. While both ventricles failed (i.e. showed elevated end diastolic pressures) on the first post-operative day, the left more severe than the right, the pressures in both chambers dropped on the second day, the right proportionately more than the left. On the succeeding two days, pressures increased slightly, but were not high, particularly on the right side. On the following day, unfortunately, the injection of this dog's usual amount of Nembutal

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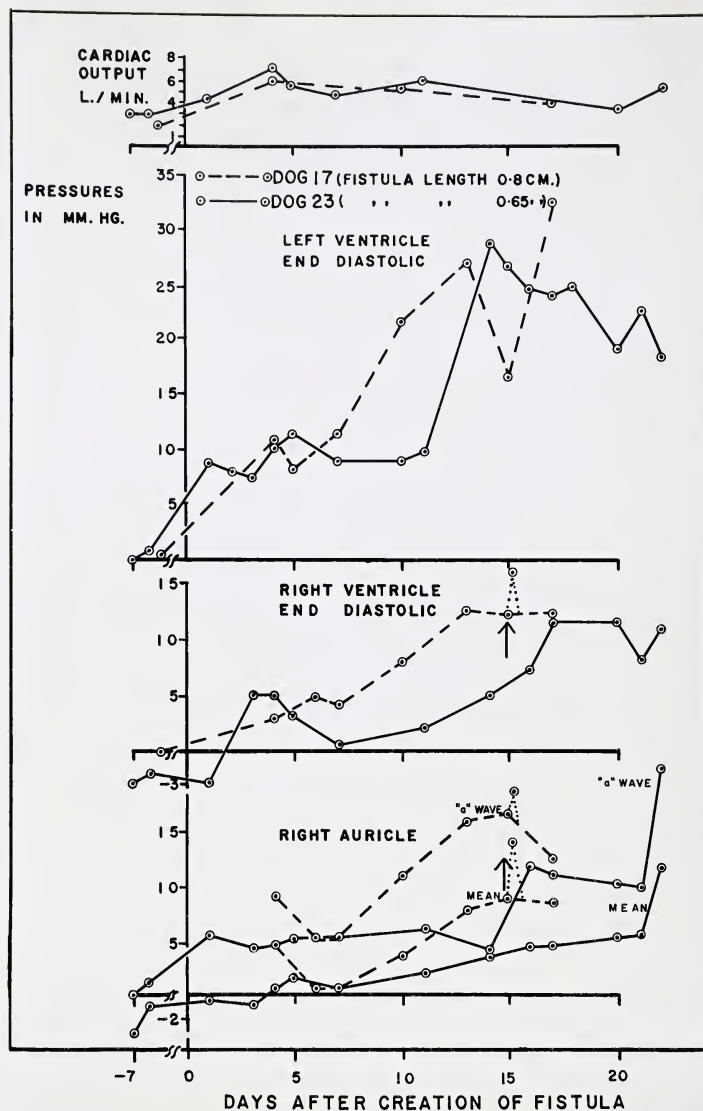


Fig. 11. Intracardiac pressure changes in 2 dogs surviving about three weeks after fistula formation. As in Fig. 10 there is parallel among the pressures, but in Dog 23, the right heart appeared to fail slightly later than the left. R.A. pressures were not measured initially in Dog 17. Arrows and dotted lines on Dog 17 curves indicate cardiovascular collapse which occurred just before L.V. puncture and was probably due to acute right heart failure.

Table XI

Dog 17: Hemodynamic Changes Following Creation of A-V Fistula.

Days	Weight in kg.	Nembutal mg./kg.	Oxygen Sat. %		Pressures in Mm. Hg.							Heart Rate	Hematocrit	Cardiac Output	Resistance in Units			
			R. V.	Carotid	R. A. Wave	R. A. Mean	R. V.	P. A.	Carotid	L. V.	Pulmonary				Peripheral			
-3	13.0	23.1	71	99			26 0	10			164 131	148	167 0.4	67	110	1.96	4.53	
0			Aorto-caval fistula 8 mm. in length.															
4	11.8	25.5	92	100	9.0	4.4	39 2.7	14		166 98	133	162 10.9 130 8.1	76	140	35	6.10	1.31	
5	12.1	8.3											140	140				
6	12.5				5.2	0.3	33 4.9	11				118 11.5	52	135				
7	12.0	12.6			5.3	0.3	49 4.2	17	38 16	21			140	140				
10	12.2	20.4	91	98.5	11.0	3.6	52 8.1	25	46 17	32	162 69	115	139 21.8	73	148	5.27	1.31	
13	12.8	15.6			16.2	8.1	59 12.8	30	54 20	38			141 27.4	77	158			
15	13.0	19.2			16.6	8.9	63 12.6	36	62 27	44	122 80	104	101 16.9	48	140	0.285		
17	12.6	21.7	86	97	12.6	8.6	61 12.7	35	54 29	41	144 80	116	142 33.2	73	145	3.88	1.80	
28	13.3	Died during injection of 5.6 mg./kg. of Nembutal.																

* Arterial pressure dropped suddenly after Cardiac output measurement.

Dog 23: Hemodynamic Changes Following Creation of A-V Fistula

Days	Weight in kg.	Numbats mg./kg.	Oxygen Saturation %		Pressure in mm./Hg.						Heart Rate	Hematocrit	Cardiac Output	Resistance in Units	
			R.V.	Carotid	R.A. Wave	R.A. Mean	R.V.	P.A.	Carotid	L.V.				Pulmonary	Peripheral
-7	12.8	31.3	69	95	0	-3.6	17 -2.9	13 5	129 99	124 0	180	45	3.12	.154	2.12
-6	13.2	26.5	73	92-95	1.4	-1.0	21 -2.2	19 7	153 119	156 0.7	180	42	3.04	.257	2.72
0	Aorto-caval fistula 6.5 mm. in length														
1	12.4	24.2	82	96	5.4	-0.5	42 -2.7	33 10	145 102	145 8.9	200	40	4.29	.238	1.64
2	12.4	15.3	—	—	—	—	—	—	—	120 8.2	180	—	—	—	—
3	12.5	26.0	—	—	4.1	-0.3	42 5.0	41 6	147 92	142 7.7	180	—	—	—	—
4	12.9	29.1	85	98	4.4	0.3	36 5.1	32 5	112 64	119 10.3	170	30	7.17	.134	.70
5	13.4	28.0	84	96	5.2	1.4	36 3.2	30 12	136 82	129 11.5	180	27	5.15	.233	1.27
7	13.2	24.5	86	96	5.4	0.4	31 0.4	—	122 76	113 9.0	175	29	4.65	—	1.25
10	12.6	27.3	—	—	—	—	—	—	—	87 9.3	160	—	—	—	—
11	13.1	30.5	87	97	6	1.3	41 2.0	32 14	126 83	122 10.1	175	27	6.01	.200	1.05
14	13.0	23.2	—	—	4.2	3.3	40 5.2	—	120 79	119 29.1	—	—	—	—	—
15	13.1	20.6	—	—	—	—	—	—	—	120 27.0	—	—	—	—	—
16	13.6	22.1	—	—	12.0	4.5	41 7.5	40 24	140 93	135 25.0	180	—	—	—	—
17	13.2	19.0	—	—	11.2	4.5	45 11.8	41 21	—	129 24.5	162	—	—	—	—
18	13.6	14.7	—	—	—	—	—	—	—	103 25.0	160	—	—	—	—
20	13.6	14.9	* 48	57	10.3	5.1	45 12.0	40 20	121 59	112 19.6	140	33	3.7	.486	1.49
21	13.4	22.1	—	—	10.1	5.2	42 8.4	40 23	—	104 23.0	164	—	—	—	—
22	13.9	10.3	22	34	21	11.8	37 11.3	35 16	109 41	112 18.7	150	32	5.2	.312	0.92
22	Died 1 hour after the above determinations were performed														

* S.V.C. saturation 43%

caused sudden death; it seems likely that barbiturate depression of the failing myocardium was the causative factor. At autopsy, there was marked congestion of the entire right lung and the lower lobe of the left lung, with edema fluid present within alveoli in some areas. A moderate amount of frothy edema fluid was present in the trachea. The liver showed moderate centrilobular congestion and atrophy. The spleen was not congested, but in fact appeared contracted, indicating that barbiturate dilatation of this organ did not have time to occur, so sudden was death from (left?) heart failure.

Dogs which survived three weeks. These findings are presented in Tables XI and XII and Fig. 11. Pressures in Dog 17 were not measured until the fourth post-operative day, at which time both ventricles were in failure, the left apparently more marked than the right. At this point it should be mentioned that the next points plotted in Fig. 11 are not simultaneous. Thus, on the fifth day the L.V. pressure had dropped slightly (no R.V. reading) and on the sixth day the R.V. pressure had increased (no L.V. reading). This might suggest an increased burden on the right ventricle as a result of increased L.V. pressure. On the seventh day, however, the L.V. and diastolic pressure increased and the pulmonary artery pressure increased (Table VI), while the R.V. and R.A. pressures decreased. Following this, pressures on both sides of the heart increased sharply, the left again more than the right. On the fifteenth day, marked by arrows in Fig. 11, the dog's carotid artery pressure dropped suddenly just after the cardiac output determination. Pressures on the right side of the heart had suddenly increased. Left ventricular puncture revealed a considerable fall in end diastolic pressure. These findings suggest that for some reason, the dog went into sudden right heart failure, decreasing the left ventricular load and decreasing the cardiac output (and therefore the systemic arterial

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pressure). Two days later, pressures on the right side of the heart had returned to the previous levels, while the L.V. pressure had increased considerably. No readings were obtained during the following ten days, during which time the dog developed massive edema of the legs and abdominal wall. He died very suddenly after injection of a small dose of Nembutal. At autopsy, in addition to the marked peripheral edema, there was marked bilateral hydrothorax and marked ascites. The lungs were very congested, and erythrocytes were scattered throughout many alveoli, but there was no obvious edema. The liver showed moderate congestion but there was little centrilobular atrophy. Other organs were not remarkable, except for narrow fibrous tracts in the left ventricular muscle due to previous needle punctures. This dog, then, showed signs of bilateral ventricular failure, but organic changes were not as marked as in other dogs, except for the massive peripheral edema. The longer survival of this dog might account for the variation in changes, as compared with animals which went into failure more acutely. Incidentally, Fig. 11 shows the gradual decrease in cardiac output which paralleled the severity of failure.

Dog 23 went into left ventricular failure within twenty-four hours of creation of the fistula, but the right ventricular pressure remained normal. The elevation of right auricular systolic pressure ("a" wave) was doubtless due to the increased return of blood to the heart via the shunt. By the third post-operative day, the right heart was also in failure. Following this, the L.V. pressure increased, while the R.V. pressure decreased; then the L.V. pressure decreased somewhat. These events, as well as the tendency for the left ventricle to fail slightly earlier than the right, and much more severely, suggest that the right heart accommodates to volume loads better than the left heart. Further evidence for this is seen in this dog's further course: left ventricular end diastolic pressure rose sharply, followed by the right heart pressure. At the peak of the R.V. pressure, L.V.

pressure declined somewhat. This may have been due to increased pulmonary resistance "protecting" the left ventricle and adding burden to the right, since on the twentieth day, the cardiac output had decreased from previous values while the pulmonary resistance had more than doubled (see Table XII). The severity of failure and the multitude of changes which were occurring at this time is indicated by the arterial and venous oxygen saturations, 57% and 43% respectively. The pressure and cardiac output changes on the last day were presumably due to anoxia secondary to marked heart failure and lung congestion. This interpretation is supported by the autopsy findings of marked congestion of the lungs, with numerous focal hemorrhages and areas of edema, and severe centrilobular congestion and atrophy of the liver with occasional foci of necrosis. The myocardium of this dog was similar to that of Dog 15, with several small areas of very recent necrosis due to needle puncture; these may have been terminal since in the last determinations, several left ventricular punctures had been performed to observe the effects of strophanthin administration.

Dog 19. A large (13 mm.) fistula was constructed in this dog and onset of failure was prompt, although there appeared to be a lag on the right side. L.V. end diastolic pressure rose rapidly, but then pressures on both sides of the heart declined. Unfortunately, the dog was not catheterized every day, but the L.V. puncture findings are recorded (Fig. 12). At this time, the dog was losing weight, refused to eat, and drank little. He was tube fed under anesthesia twice. On the ninth day, the reason for the behavior became apparent when he passed considerably bloody stool. Intussusception was suspected. A slow intravenous of saline was administered, resulting in a marked rise in L.V. end diastolic pressure. This change indicated that the dog's myocardium was severely compromised, but L.V. pressure had not markedly elevated because of a presumably decreased blood volume; however,

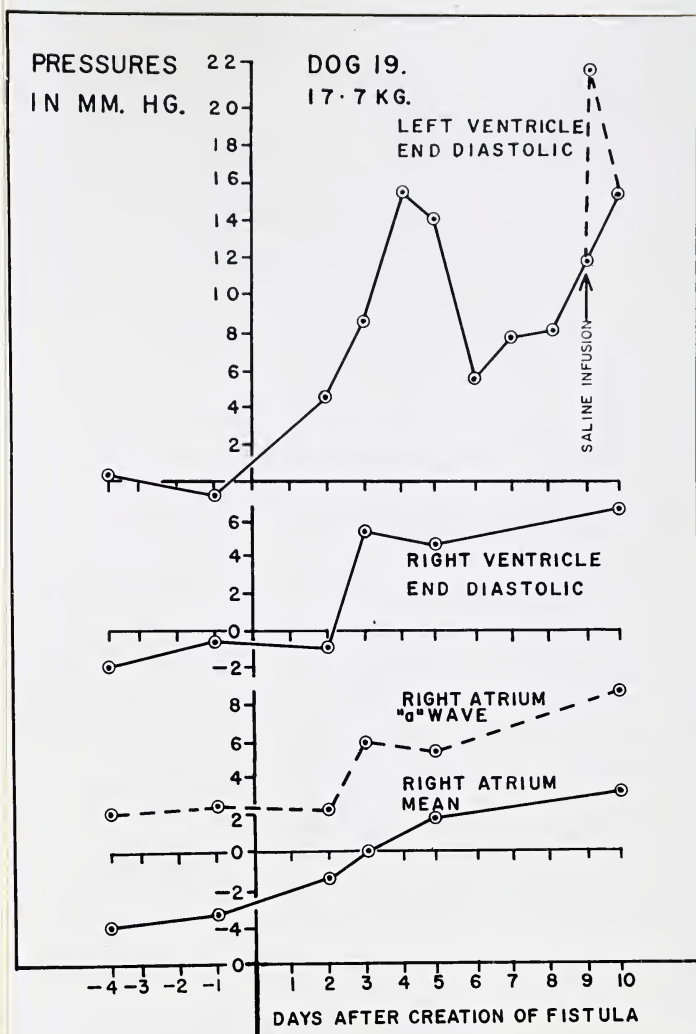


Fig. 12. Intracardiac pressure changes in Dog 19 after creation of large A-V fistula (13 mm. in length). This dog lost 36% of his body weight due to bowel intussusception, weighing 11.3 kg. at death, probably accounting for the decrease in L.V. end-diastolic pressure during days 5 - 8. The status of the myocardium was indicated by the marked increase in pressure following slow infusion of 200 c.c. saline on day 9. As with Dog 23 (Fig. 12), the right heart appeared to fail somewhat slower than the left after the creation of the fistula.

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Dog 19: Hemodynamic Changes After Creation of A-V Fistula

Days	Weight in kg.	Nembutal mg./kg.	Oxygen Saturation %				Pressures in mm. Hg.						Heart Rate	Hematocrit	Cardiac Output	Resistance in Units				
							R. A. "a" Wave	R. A. Mean	R. V.	P. A.	Carotid	L. V.				Pulmonary	Peripheral			
			S. V. C.	R. V.	Carotid															
-4	17.5	42.9	70	—	94	2.1	-4.1	33	24	143	139	69	120	40	2.35	.281	3.18			
-1	17.7	45.2	—	72	93	2.5	-3.4	36	—	160	156	76	136	48	3.3	—	2.22			
0	Aorto-caval fistula 13.0 mm. in length																			
2	16.0	17.1	—	—	—	2.6	-1.4	44	35	—	129	54	156	—	—	—	—			
3	16.3	18.4	—	87	97	6.	0	51	43	159	138	57	150	33	4.814	.386	1.39			
4	15.5	—	—	—	—	—	—	—	—	—	152	65	150	—	—	—	—			
5	15.3	16.3	—	—	—	5.3	1.8	54	49	—	146	65	140	—	—	—	—			
6	15.0	6.6	—	—	—	—	—	4.7	19	—	137	62	135	—	—	—	—			
7	14.8	10.1	—	—	—	—	—	—	—	—	128	58	140	—	—	—	—			
8	14.8	6.8	—	—	—	—	—	—	—	—	119	47	138	—	—	—	—			
9	14.1	8.9	Before intravenous saline														117	45	125	
			After slow intravenous 200 c.c.														138	61	140	
10	14.2	14.0	72	91	99	8.7	3.2	54	50	155	131	59	140	30	5.31	.384	1.05			
12	11.3	Died with intussusception of intestine with gangrene and early peritonitis.																		

intravenous fluid increased the blood volume enough to greatly increase the L.V. pressure. On the following day, the pressure increased somewhat on both sides of the heart. At death, there was an extensive large bowel intussusception with gangrene and early peritonitis. All chambers of the heart were dilated. L.V. needle punctures had left two or three narrow zones of myocardial necrosis with fibrin exudate and infiltration by occasional leukocytes. The lungs were only slightly congested, despite the considerable increase in L.V. and diastolic pressure which had existed in life; this would indicate that blood volume per se plays an important part in causing pulmonary congestion and edema during heart failure. The liver showed slight centrilobular congestion and atrophy.

Dogs which survived three to four months. Dog 22 (Fig. 13) exhibited several interesting features. On the first post-operative day, she showed elevation of pressure in both ventricles, more marked on the left. A slight fall then occurred, less marked on the left. Atrial pressure remained normal. The end diastolic pressure then increased in both ventricles, and in the right atrium. On the twelfth day, a peak in pressure in both ventricles was accompanied by a drop in cardiac output with increased pulmonary and total peripheral resistance, in the face of an increased blood volume as suggested by previous depression of hematocrit. These findings may have been due to barbiturate effect; certainly the depression in cardiac output is reflected by the decreased venous oxygen saturation (Table XIV). During the following two weeks, pressures on both sides of the heart rose. The isolated points plotted in Fig. 13 (left ventricular punctures unaccompanied by right heart catheterization) show that the left ventricular diastolic pressure was high. Subsequent events, however, suggest that the heart of this dog was actually in borderline failure rather than in actual uncompensated failure. Thus, on the 33rd day, because of jugular vein thrombosis, surgical exploration was carried out to determine the patency of the superior

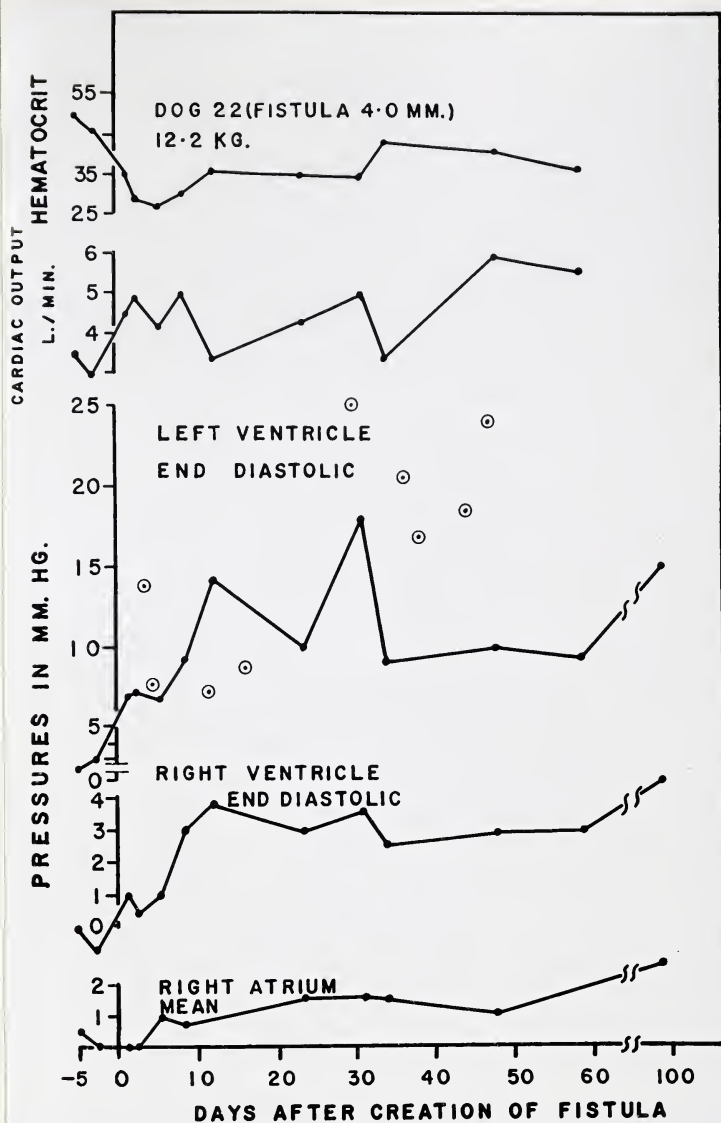


Fig. 13. Again note the parallel pressure changes between the left and right heart, although in this dog the changes are of greater magnitude in the left ventricle. Unplotted points on the left ventricle graph are isolated readings obtained on days when right heart catheterization was not performed; these points were not incorporated in the curve so the parallel among curves would be more easily visible.

Table XIV

Dog 22: Hemodynamic Changes After Creation of A-V Fistula

199.

Days	Weight in kg.	Nembutal mg./kg.	Oxygen Saturation %				Pressures in mm. Hg.						Heart Rate	Hematocrit	Cardiac Output	Resistance in Units					
			Jugular	S.V.C.	P.A.	Carotid	P.A. Wave	P.A. Mean	R.V.	P.A.	Carotid	L.V.									
-5	12.4	28.2	—	93	84	100	2.2	0.4	30	12	28	18	158	140	155	70	168	50	3.48	.310	2.41
-3	11.8	31.8	—	87	81	98	1.5	0	32	11	27	17	166	148	163	74	160	46	2.92	.349	3.04
0	Aorto-caval fistula 4.0 mm. in length																				
1	11.8	33.9	69	70	87	98	3.1	0	42	15	40	21	176	150	173	83	180	35	4.46	.282	2.02
2	11.8	36.0	—	62	83	94	3.2	0	38	15	36	22	152	127	156	75	166	28	4.81	.274	1.58
3	12.2	16.4	—	—	—	—	—	—	—	—	—	—	—	—	98	51	134	—	—	—	—
4	—	—	—	—	—	—	—	—	—	—	—	—	—	—	90	43	130	—	—	—	—
5	12.1	28.9	81	—	87	98	3.4	0.9	38	17	30	21	159	128	154	78	170	26	4.17	.302	1.84
8	11.8	33.9	61	81	86	96	3.5	0.7	42	17	38	25	157	126	160	76	170	29	4.96	.302	1.52
11	11.7	21.4	—	—	—	—	—	—	47	20	37	25	151	124	147	70	180	—	—	—	—
12	11.7	27.8	55	60	85	96	—	—	3.8	—	151	124	152	124	152	72	170	36	3.36	.446	2.21
16	13.0	21.2	—	—	—	—	—	—	—	—	—	—	—	—	119	58	150	—	—	—	—
23	12.0	29.2	66	84	84	95	4.2	1.4	42	18	40	25	166	134	165	82	160	35	4.53	.346	1.86
30	12.2	24.6	—	—	—	—	—	—	—	—	—	—	—	—	153	74	150	—	—	—	—
31	11.9	21.1	—	53	81	95	4.6	1.5	43	20	39	28	162	138	157	88	154	34	5.09	.330	1.63
33	11.9	25.2	—	80	85	94	3.8	1.4	41	18	36	24	170	140	168	88	146	43	3.40	.424	2.47
36	12.2	20.5	—	—	—	—	—	—	—	—	—	—	—	—	130	64	143	—	—	—	—
38	—	—	—	—	—	—	—	—	—	—	—	—	—	—	125	61	145	—	—	—	—
44	12.6	13.9	—	—	—	—	—	—	—	—	—	—	—	—	124	58	140	—	—	—	—
47	12.2	—	—	—	—	—	—	—	—	—	—	—	—	—	141	76.4	148	—	—	—	—
48	11.8	33.9	—	64	82	94	2.9	0.8	48	21	45	31	177	144	182	94	156	41	5.87	.317	1.47
59	12.4	36.2	71	—	82	95	—	—	45	20	48	32	158	131	155	79	155	36	5.51	.348	1.43
Shortly after anesthesia, L.V. Pressures were:																					
After cardiac output, 8 mg./kg. Nembutal injected:																					
5 minutes later:																					
99	11.3	24.3	—	—	80	95	—	2.5	50	18	—	—	—	—	131	70	172	—	—	—	—
Killed																					

Shortly after anesthesia, L.V. Pressures were:

After cardiac output, 8 mg./kg. Nembutal injected:

5 minutes later:

99	11.3	24.3	—	—	80	95	—	2.5	50	18	—	—
	Killed								4.5			

Δ left iliac vein

* saturation at site of fistula

x experiments performed after cut-down onto lower S.V.C., entailing blood loss and stimulation of dog.

vena cava; this procedure was accompanied by pain stimulation, since anesthesia was not in surgical planes, and moderate blood loss. End diastolic pressures and cardiac output dropped considerably. Subsequent isolated left ventricular punctures yielded much higher L.V. pressures, although barbiturate depression of the myocardium may have affected these values since L.V. punctures were generally carried out under somewhat deeper anesthesia, i.e., sooner after induction of anesthesia than when complete determinations were carried out. On the forty-eighth day, the superior vena cava was again catheterized after surgical exploration, with less blood loss than previously but again with some pain stimulation. End diastolic pressures were again lower, but cardiac output was much higher. In subsequent experiments, this dog was catheterized via the left iliac vein, with little blood loss or excessive stimulation, yet values for end diastolic pressures and one cardiac output estimation were relatively unchanged. However, the borderline status of the myocardium is suggested by the effects of Nembutal (Table XIV, 59th day): early in the experiment, under somewhat deeper anesthesia, L.V. end diastolic pressure was 21.4 mm. Hg.; by the time of cardiac output determination, this pressure had dropped to 9.2 mm. Hg. Nembutal 8 mg./kg. body weight was administered, elevating the end diastolic pressure to 22.3 mm. Hg. (Fig. 9); five minutes later, the pressure had dropped again, to 16.9 mm. Hg. By the 99th day, left and right ventricular and right atrial mean pressures were all elevated. The dog was killed by Nembutal injection and autopsy performed. The lungs were not congested, nor did the liver appear enlarged. There was no hydrothorax nor ascites. There was no visible fibrosis in the myocardium as a result of cardiopexy or multiple L.V. Punctures.

This dog, as others already mentioned, exhibited the parallelism

in end diastolic pressure changes between the ventricles. Again the L.V. pressure changes were more marked than those in the right ventricle.

The parallelism between ventricular end diastolic pressures is particularly striking in the case of Dog 26 (Fig. 14), probably being more apparent than in the previous figures because few left ventricular punctures were performed unaccompanied by right heart catheterization. Again, there is elevation of pressures immediately post-operatively, then a drop in pressures on both sides, then an increase on both sides to a fairly stable level for nearly two months. Unlike the initially swinging ventricular pressures, R.A. mean pressure remained virtually normal for the first six days after creation of the fistula. Regarding the cardiac output during the initial period, there was an immediate increase post-operatively, and then a progressive increase, while the hematocrit fell, probably due to increased blood volume. The peak of this secondary cardiac output rise, the lowest hematocrit value, and the upward swings in ventricular pressures occurred at the same time. Following a two-month period of relative stability, on the 71st day the cardiac output and ventricular end diastolic pressures increased considerably. If it is true that Nembutal anesthesia may place the dog's circulatory system at moderate to exercise levels of activity, then it is possible that these values were due to the anesthetic. Pressures later dropped somewhat, although not to previous levels, then rose slightly to the 118th day, when the dog was killed with Nembutal. Autopsy disclosed no lung congestion. There was very slight patchy fibrosis in the anterior papillary muscle of the left ventricle.

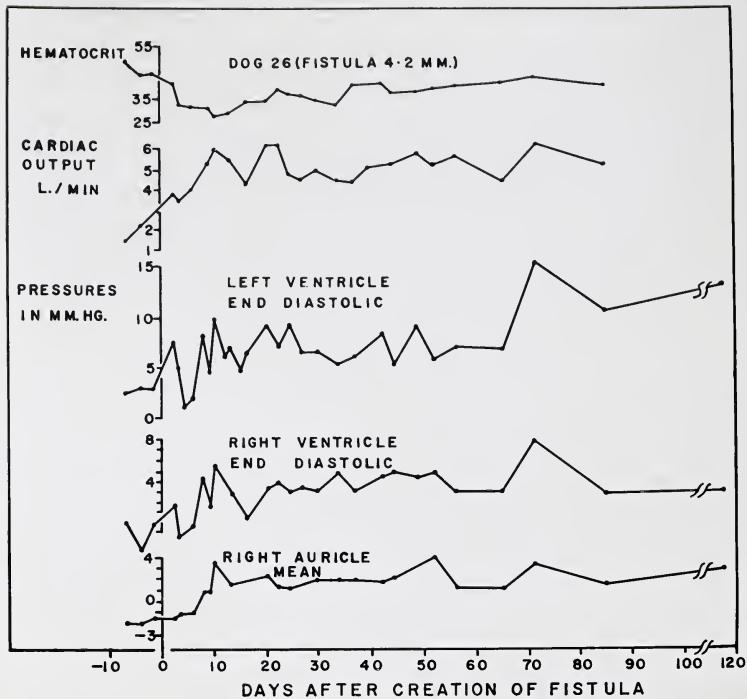


Fig. 14. Striking parallel exists among the pressure curves throughout. Note early inverse relationship between hematocrit and cardiac output, probably representing an increase in plasma volume. Subsequently, hematocrit gradually rises. Cardiac output parallels end-diastolic pressure changes.

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Table XV

Dog 26: Hemodynamic Changes After Creation of A-V Fistula

Days	Weight in kg.	Nembutal mg./kg.	Oxygen Saturation %				Pressures in mm. Hg.							Heart Rate	Hematocrit	Cardiac Output	Resistance in Units	
			Jugular	S.V.C.	P.A.	Carotid	P.A. Wave	P.A. Mean	R.V.	P.A.	Carotid	L.V.						
-7	14.8	30	—	—	88	103	0.4	-2.7	32 -0.2	25 4	199 140	164 2.6	77	168	51	1.31	.550	7.52
-4	—	23.6	—	82	86	105	0.7	-2.6	32 -2.7	24 1	206 161	182 3.1	90	120	43	2.04	.322	5.33
-1	14.8	28.7	—	—	—	—	0.2	-1.8	31 -0.2	26 2	214 174	189 2.9	92	125	45	—	—	—
0	Aorto-caval fistula 4.2 mm. in length																	
2	14.3	43.7	—	64	84	99	1.8	-1.8	47 0.7	35 7	190 116	153 7.6	82	173	40	3.76	.287	2.44
3	14.3	29.7	—	67	79	94	0.2	-1.6	40 -1.1	29 6	161 100	129 4.8	71	176	32	3.54	.260	2.19
4	14.8	15.5	—	—	—	—	—	—	—	—	—	—	56	160	—	—	—	—
6	14.0	39.3	—	79	85	98	1.5	-1.3	38 -0.3	22 10	184 118	152 1.8	75	185	30	3.81	.236	2.39
8	—	—	—	—	—	—	3.7	0.9	41 4.3	32 6	—	—	53	145	—	—	—	—
9	14.5	34.5	69	—	88	98	3.2	0.8	42 1.6	27 9	174 103	144 4.8	87	143	31	5.46	.209	1.58
10	14.9	28.5	72	—	82	99	6.8	3.6	52 5.5	42 17	189 122	159 10.0	86	170	27	5.94	.273	1.61
12	14.5	22.4	—	—	—	—	—	—	—	—	—	—	60	142	—	—	—	—
13	14.8	25.3	60	—	86	98	4.08	1.6	46 2.8	34 14	192 116	158 6.9	89	170	29	5.62	.246	1.69
15	—	—	—	—	—	—	—	—	—	—	—	—	40	130	—	—	—	—
16	14.1	26.6	—	76	84	96	—	—	43 0.3	32 11	187 116	157 6.4	90	166	33	4.32	.292	2.18
20	14.6	20.5	—	—	86	97	5.4	2.5	41 3.4	34 9	174 101	139 9.3	86	130	33	6.28	.191	1.33
22	14.3	21.0	66	70	84	96	3.0	1.5	47 3.8	34 11	201 126	159 7.6	104	150	38	6.25	.192	1.53
24	14.0	—	84	80	85	96	4.5	1.4	40 3.0	32 8	158 90	123 9.3	83	126	36	4.74	.228	1.56
27	—	17.5	50	45	84	96	5.4	1.8	47 3.4	41 11	175 102	141 6.8	79	140	35	4.64	.284	1.82
30	—	—	65	67	85	95	—	—	42 3.1	34 10	183 115	146 7.0	84	135	33.5	5.19	.243	1.69
34	—	—	64	82	83	96	4.8	1.8	44 4.8	30 12	157 94	133 5.6	84	132	32	4.64	.272	1.72
37	14.7	20.4	73	67	83	94	5.2	1.7	41 3.0	29 10	168 102	136 6.2	83	158	39	4.41	.245	1.85
42	14.6	22.3	70	64	87	98	4.2	1.8	48 4.5	37 19	189 118	155 8.5	99	160	40	4.90	.318	1.90
44	14.4	27.8	70	66	80	91	6.4	2.1	49 4.8	39 7	174 106	138 5.2	87	155	36	5.29	.261	1.57
49	14.4	20.8	66	62	82	95	—	—	40 4.5	36 10	160 102	127 9.2	87	125	36	5.76	.240	1.52
52	15.2	23.0	72	62	80	94	8.5	4.3	45 4.8	32 12	176 110	147 5.8	92	156	38	5.28	.238	1.67
56	14.3	28.0	71	45	83	95	4.0	1.2	51 2.9	39 16	181 117	144 7.5	91	162	39	5.76	.250	1.50
65	14.6	20.5	69	60	80	88-94	4.2	1.1	46 3.0	39 14	182 110	148 7.1	91	155	40	4.36	.344	2.04
71	14.8	20.3	60	68	79	93-96	8.0	3.8	45 8.0	39 12	196 124	154 15.6	104	140	42	6.18	.233	1.50
85	13.8	25.4	70	63	76	87-92	3.9	1.5	49 2.7	38 11	161 93	132 11.8	81	130	39	5.18	.277	1.53
118	13.7	25.5	67	54	76	90-93	5.6	3.2	43 3.1	39 17	172 102	138 13.1	90	140	—	—	—	—

Killed

Other Changes. Other changes following creation of a fistula noted in these experiments have been described by other authors. These include: (a) a further increase in cardiac output after the immediate post-operative increase,⁴ apparently due to blood volume increase accompanied by end diastolic pressure increase; (b) increase in pulmonary artery pressure due to increased cardiac output;³ (c) decreased hematocrit, partially due to operative blood loss and partially due to increased blood (i.e. plasma) volume; the hematocrit gradually rises, but in our dogs never returned to pre-operative levels; (d) decreased venous oxygen saturation due to decreased blood supply to other tissues as a result of the shunt; this was less noticeable if the fistula was small; (e) with increasing severity of failure, there followed a decrease in cardiac output, decrease in venous oxygen saturation, increases in total pulmonary and peripheral resistance, and even decreased arterial oxygen saturation; (f) digitalis compounds do not influence intracardiac pressures, or the course of failure. Adrenal gland enlargement³⁰ was not noted, nor did our dogs develop subacute bacterial endocarditis or renal lesions.³ There was no definite myocardial hypertrophy,⁴¹ although dilatation was usually present.

DISCUSSION

The energy cost in terms of oxygen consumption by the heart is less for output work than for the same amount of pressure work, so that opening of an A-V shunt need not be accompanied by increased myocardial oxygen consumption. Youmans has suggested that the human heart may respond to an A-V fistula as any normal heart would respond to lowered peripheral resistance and increased venous load, and that myocardial weakness may not occur. Therefore the circulatory failure that develops with high cardiac output in the presence of a fistula is probably most often congestive in origin rather than myocardial.

Iseri et al. stated that congestive failure may occur in beri-beri (also high cardiac output disease) without myocardial failure. This absence of "myocardial failure" may explain the lack of effect of digitalis compounds on the course of high output congestive circulatory failure. However, the use of the term "myocardial failure" would not appear to be quite correctly used by these authors, perhaps because only in recent years has it been appreciated that there are various kinds of heart failure. The number is not known, nor are definitions anywhere near precision. Biochemists speak of reduced cardiac efficiency accompanied by "disturbance in energy production" (e.g. beri-beri) and "disturbance in energy utilization" (e.g. low output or clinical "congestive" heart failure). In the latter, it would appear that the failing heart has partially lost its ability to convert energy derived from processes of energy production into useful work, i.e. there is deficient utilization of energy. On the basis of coronary catheterization studies, the failing heart utilizes various substrates normally, but with increased work load (e.g. exercise) there is a rise in oxygen consumption.^{2,36}

In the presence of cardiac dilatation, there is evidence that changes in amount (decrease) and quality of actomyosin occur, probably due to partial dissociation or depolymerization of contractile protein.¹ There is ample evidence that cardiac dilatation occurs with opening of an A-V shunt, so that additional metabolic factors must be operative to account, for example, for the response of some types of heart failure to digitalis while other types do not.

Katz²⁷ understated the problem when he wrote, "The mechanical efficiency of the failing heart changes in a very complex fashion, all details of which are not clearly understood".

In our experiments, disregarding biochemical problems, interpretation in some ways is difficult because daily x-ray studies to determine heart size

were not done, and the blood volume determinations, for reasons not yet completely solved, were grossly variable. However, the frequent pressure measurements indicated that several of these dogs went into failure virtually immediately. It is inconceivable that their blood volumes could have increased sufficiently overnight, following a blood-losing operation, to develop "congestive" failure. We must assume that they developed "myocardial" failure of some sort, although doubtless congestion (i.e. increased blood volume) soon supervened and added to the circulatory burden. Hematocrit depression indicated increases in plasma volume, although it is realized that the hematocrit does not immediately reflect such increases, in humans at least.³³ The decrease in hematocrit may have accounted for some of the increased cardiac output; a hemoglobin level of 7 gm. per cent in dogs is required to increase the output.²⁰

It is unlikely that hematocrit depression was great enough to affect the oxygen supply of the myocardium, since other studies show that it is only at hematocrit values of 23% or lower that ventricular function is depressed.⁵ However, there is another factor which may have affected the myocardium, the decreased diastolic arterial pressure, which accompanied by the tachycardia which follows fistula formation, may well have caused some myocardial ischemia. It has long been known that the coronary blood flow occurs mostly in diastole, and low diastolic pressure accompanied by a shortened diastolic interval might well exert a combined detrimental effect. This might explain the sudden onset of bilateral ventricular failure in our dogs. Even a slight degree of impaired blood supply, in the presence of increased cardiac work, might be sufficient to impair myocardial function. The lack of change in our figures for heart rate may have been due to the vagal blocking effect of Nembutal. We have mentioned the changes in levels of end diastolic pressure which occurred with varying levels of anesthesia. Cardiac output depression would aggravate any impairment of coronary blood flow. This would be additive to the

Nembutal retardation of ventricular relaxation and elevation of mechanical impedance (and therefore decreased stroke output) which occurs in well-oxygenated experimental hearts.^{6,7} Such a sequence of events might explain the sudden death which occurred in two of our dogs following injection of Nembutal.

The above speculations provide an explanation for the rapidity of exitus which occurs in dogs with large aorto-caval fistulas, as well as the rapid onset of ventricular failure which occurred in our dogs. Such an explanation indicates that dogs with large aorto-caval fistulas experience a different course from animals (and humans) with smaller fistulas; the latter may then develop the "congestive" syndrome reviewed by Youmans, any subsequent myocardial failure perhaps being due to the same mechanism operative in our dogs. In this regard, some of our dogs showed a decrease in ^{aortic} diastolic pressure as failure progressed which may explain the rapid rise in ventricular end diastolic pressures which occurred.

Incidentally, the complicating abdominal pathology in Dog 19, probably preventing an increase in blood volume, seems added evidence that some of our dogs, at least those that died rapidly, died primarily of myocardial failure rather than of congestive failure. The somewhat variable autopsy findings would be at least partially explained by which type of failure was present in greater degree, although it is realized that the acuteness and severity of failure would also influence such findings as centrilobular liver congestion and necrosis. In this regard, too, if some of these dogs died primarily of myocardial (hypoxic) failure, the presence in some dogs and not in others of muscle necrosis around needle puncture sites might be explained. One more possible factor is suggested in a paper by Guyton et al.,¹⁴ who suggested that rapid failure, with increased R.A. pressure before blood volume increase (and therefore venous pressure increase) would result in

The first of these is the fact that the system is not a simple one. It is a complex one, and it is one that is not easily understood. It is a system that is not easily understood, and it is one that is not easily understood. It is a system that is not easily understood, and it is one that is not easily understood.

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cessation of venous return. Regarding the sometimes striking parallel between R.V. and L.V. pressures which we observed, it is of interest that Ferguson et al. found that the R.V. end-diastolic pressure consistently followed the L.V. pressure in two open and two closed chest dogs receiving intravenous infusions.

The tendency to much higher L.V. than R.V. pressures in our dogs seems to be due to the greater mass and resistance to filling of the left ventricle.¹⁹ Perhaps this is why the left atrium is less distensible than the right atrium.³⁴

It has been shown in dogs that moderate changes in blood volume are accompanied by quite uniform changes in the central veins, pulmonary artery and left atrium, and the observers suggested that the lesser circulation behaves toward blood volume changes as a series of connected elastic bags. The right atrial pressure increased or decreased as the blood volume increased or decreased. These observations may be applicable to some of our experiments when the R.A. pressure did not rise with the initial rises in ventricular pressures. Perhaps, too, the swing in ventricular pressures in the first few days after fistula formation was due to interlocking mechanisms involving myocardial ischemia and then recovery, with increasing blood volume and decreasing hematocrit. Also in this regard, the demonstrations of atrial stretch receptors, which may increase urine flow when stimulated, may have been involved in this initial post-operative period.^{21, 23} It would be interesting to observe nerve impulse changes from these receptors when an A-V fistula is opened. But obviously there is a multitude of problems not yet solved by these experiments.

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